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Therapeutic Aspects on *Mycobacterium*: Mycobacterial Cell-Envelope as a Target for Drug Development

Ciamak Ghazaei[1*]

[1]Department of Microbiology, University of Mohaghegh Ardabili, Ardabil, Iran

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***Correspondence to**
Ciamak Ghazaei,
Email: ciamakghazaei@yahoo.com

Abstract
Mycobacterium tuberculosis, the causative factor of tuberculosis (TB) infections, has an atypical outer membrane mostly consisting of lipids with long-chain and branched fatty acids termed mycolic acids. These lipids establish a permeability barrier that inhibits numerous environmental solutes from entering the bacteria, making them acid-fast and enabling them to thrive in harsh environments. To meet their target, anti-TB drugs need to penetrate this layer. This review focuses on drug development initiatives that have contributed to TB drug development, lipids' roles in *M. tuberculosis* pathogenesis, and recently made fresh remarkable progress in developing novel lead chemical compounds that target their biosynthesis metabolisms. Selective bacterial membrane targeting as a promising therapeutic approach against persistent infectious diseases such as TB has been proposed in this review study.
Keywords: *Mycobacterium tuberculosis*, Bacteria, Pathogenesis, Membrane, Infectious diseases

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Introduction

After human immunodeficiency virus/acquired immunodeficiency syndrome, tuberculosis (TB) is the second most serious cause of death from a single infectious pathogen. Mycobacteria have great taxonomic diversity, worldwide impact, and unique cell walls and cell envelop. *Mycobacterium tuberculosis*, the causative agent of TB causing high morbidity and mortality, is among the most studied bacteria belonging to the *Actinobacteria* phylum. *M. tuberculosis* is the leading cause of mortality worldwide, thus the World Health Organization has announced that combating this bacterium is a top priority.[1] This global burden has prompted advancements in diagnostics, effective innovative treatments, and healthcare provision. However, the rise of the *M. tuberculosis* multidrug-resistant strain challenges these advances, necessitating more knowledge of *M. tuberculosis* biochemistry and pathogenicity to find new anti-tubercular pharmaceutical options and targets.[2] The cell envelope of mycobacteria is a proven drug target for TB medicines.[3] Consequently, this topic has undergone extensive research throughout the past two decades. Most structural chemical components of the *M. tuberculosis* cell wall and their biosynthetic processes have been resolved because of advances in genomic and molecular approaches. Ongoing drug discovery endeavors have revealed diverse chemotypes that can block several associated components of mycolic acid formation, which also have the potential for further development.[4]

Mycobacterium tuberculosis Cell-Envelope Architecture

The architecture of the mycobacterial cell wall distinguishes it from the other cell walls of bacteria. Mycobacteria are enclosed in a double membrane cell envelope with an abundance of lipids. Lipids are estimated to make up 60% of the cell envelope of mycobacteria, relative to 20% in gram-negative species' cell envelope. Several models have been presented for mycobacterial cell envelopes. The cell envelope is categorized into three domains in one description; an outer layer which is a capsule mostly comprised of proteins with small proportions of carbohydrates and lipids, and a triplet cell wall with covalently bonded arabinogalactan (AG)-peptidoglycan (PG) complex in their outer membranes.[5]

The plasma membrane, which appears to be typical of bacterial membranes, is the innermost layer. The cell wall "core" present outside the plasma membrane is PG. Heteropolysaccharide AG is covalently attached to it. Its esterification into α-alkyl and β-hydroxy at its nonreducing ends takes place, and "free" (noncovalently bound) lipids and lipoglycans intercalate inside this lipid environment. The leaflets of a relatively impermeable bilayer formed by mycolic acids at the core of the cell wall and available

free lipids give mycobacteria their typical resistance to the development of various treatments.[5] Finally, outside of *M. tuberculosis*'s outer membrane, there was a loosely linked capsular-like structure.[6] Even though mycobacteria are Gram-positive bacteria, they have a cell envelope along with an outer membrane and periplasmic space. The cell envelope of mycobacterial has distinctive architecture and composition. It makes a strong permeability barrier to external agents and is an essential component of the overall drug mycobacteria phenotype.

Role of Mycobacterial Cell Envelope

The mycobacterial cell envelope crucially contributes to the physiology of bacteria and plays a protective role for bacteria against hostile environments, assisting the transport of solutes and proteins across membranes and receptor attachment and providing mechanical resistance to cells.[7,8] Different chemical constituents present in the mycobacterial cell envelope contribute to the biological properties of mycobacteria, helping in their pathogenicity, cell growth, host-pathogen interactions, and advanced drug resistance mechanisms against many therapeutics to persist mycobacterial infections.[9-12]

Peptidoglycans and Arabinogalactan

The dynamic structure of PG plays a significant role in bacterial cell growth and cellular communication process and triggers the host immune response.[13] Modifications that occur in the peptide fragment of PG weaken the effectiveness of antimicrobials such as antimicrobial peptides (AMPs), lysozyme, and cell-wall targeting antibiotics.[14,15] L- and D-amino acids -cross-links in mycobacterial cell help in maintaining cell integrity and producing dormancy in mycobacteria.[16,17] AG is another chemical constituent of the mycobacterial cell wall which plays a significant role in the pathogenicity of *M. tuberculosis*, aiding mycobacterial infections.[18]

Mycobacterium tuberculosis lipid's Role in Pathogenesis

The outer membrane and *M. tuberculosis* capsular lipid, which are found at the bacterium-host interface, play a key role in regulating host-pathogen interactions. All mycobacterial species synthesize various *M. tuberculosis* lipid components such as isoprenoid lipids, phosphatidylinositol mannosides (PIMs), and mycolic acids, which are required for growth. Anti-TB medicines, as well as a number of other lead compounds in development, target the production of some of these lipids.[19]

Mycobacterium tuberculosis enters host macrophages and dendritic cells (DCs) primarily through phagocytic receptors such as complement receptors or C-type lectins, including Mincle, mannose receptor, and DC-specific intercellular adhesion molecule-3-grabbing non-integrin. Glycolipid PIMs and mannose-capped lipoarabinomannan (ManLAM) are two of the most common glycolipids that mediate *M. tuberculosis*'s associations with these receptors.[20] *M. tuberculosis* is found in phagosomes that do not combine with lysozymes when inside phagocytic cells. It secretes a large number of proteins and lipids that circulate inside the cell and may be discharged through exocytosis. These molecules influence the secretion, apoptosis, and T-cell activities of pro- and anti-inflammatory cytokines, the generation of foamy macrophages, and the formation of granuloma by non-participating antigen-presenting cells, and modulate the immune function of the host cells.[21-24] Many *M. tuberculosis* lipids, particularly diacylated versions of sulfolipid, mycolyl lipids, and ManLAM serve as antigens for immunological recognition and are displayed to T cells by MHC-I-like CD1 family molecules. A few of these lipids could be used as subunit vaccines in the future.[25]

Various *in vitro* and *in vivo* studies clearly support the crucial role of phthiocerol dimycocerosates (PDIMs) and trehalose dimycolates (TDMs) in TB pathogenesis.[26] Considering that no particular virulence factor is responsible for any of *M. tuberculosis*'s pathogenic traits, compensating mechanisms within specific lipid families or cell ligands are proven to occur in this regard.[27] Lipids such as (iso)-tuberculosinol and tuberculosinol are uniquely found in pathogenic mycobacteria (*M. tuberculosis*) and have a distinct phenotype which protects bacteria from phagocytosis inside their human host. From a mechanistic approach, it can be difficult to conclude that a lipid has a direct influence on a certain host function. This is due to the importance of lipids in the structure and cell envelope permeability, as well as their potential interactions with the host. As a result, a lack of their production will not only make *M. tuberculosis* more vulnerable to the host's defense mechanisms such as PDIMs but also influence *M. tuberculosis*'s protective ability against oxidative stress. It could also have a serious impact on how other immune-modulating antigens are displayed on the cell surfaces and how they interface with the host's immune functions.[26,27]

The Membrane of Mycobacteria as a Potential Drug Target

Significant arguments indicate that bacterial membranes are suitable targets for drug-resistant and persistent microorganisms. All organisms, whether in replicating or non-replicating mode, rely on a functional and physically viable membrane to survive. Furthermore, the membrane participates in essential functions such as nutrition transport and energy transduction metabolisms via respiratory chain enzymes. Approximately one-third of cellular proteins concentrate inside their boundaries. Agents that interrupt the membrane would disturb lots of new underlying targets and processes that sustain them. Moreover, the deadly pleiotropic effects of membrane disruption would severely hamper organisms' ability to

develop resistance.[28]

Membrane targeting agents are grouped into two categories. In the first category, agents make contact with the membrane bilayer of bacteria to alter its architectural structure and functionality. The physicochemical features of these agents that are cationic amphiphiles include lipophilicity and a state of having positive charge that is typically linked with nitrogen. Lipophilicity is essential for incorporation into the membrane's lipid-rich matrix, whereas the positively charged state encourages specific storage within bacterial membranes, which, In contrast to mammalian membranes have many negatively charged groups such as phospholipids or polyanionic surface groups.[29] In the second category, membrane targeting agents can inhibit membrane-bound proteins, including enzymes responsible for energy production or cell wall formation, from performing their functions. These agents could be cationic amphiphiles or non-cationic amphiphiles. Their actions on the membrane may be indirect, including Q203, which is a clinical candidate that binds to the cytochrome bc1-aa3 super complex in mycobacteria.[30-32] According to Goldman,[29] the phenotypic analysis of chemical libraries for TB has resulted in the selection of drugs that inclined toward the membrane target.

Anti-tubercular Drugs Targeting Mycobacteria Cell Wall Biosynthesis Pathways

The survival of mycobacteria in the host depends on the cell wall's low permeability. Many anti-tubercular drugs now block enzymes responsible for cell wall production. As a result, enzymes responsible for the biosynthesis of these cell wall components of mycobacterial and the enzymes needed for their attachment could be promising therapeutic targets.[33]

A foundation of TB treatment is targeting the cell wall of mycobacteria and its outer membrane biosynthesis. Novel compound classes are developing because of forward genetics applications and target-based discovery techniques. It is becoming efficient at interrupting protective barriers, leading to a decrease in treatment times and the possibility of drug resistance.[34] Several potential new agents and targets in the biosynthesis of mycobacterial cell wall pathways have been discovered recently (Table 1).

Role of *Mycobacterium tuberculosis* Cell-envelope Lipids in Drug Discovery

The specificity and treatment-related success of both first- and second-line TB medicines such as isonicotinic acid hydrazide (INH) and ETH, which limit the biosynthesis of mycolic acids, and ethambutol, which prevents ManLAM and AG arabinan domains, are due to the diversity, distinctive structures, and important roles performed by the lipids of the cell envelope in *M. tuberculosis* physiology and pathogenicity.[7] Furthermore, pyrazinamide has been found to be a fatty acid synthase I (FAS-I) inhibitor. Considering the rise in multidrug resistance, TB drug discovery efforts have stepped up in recent years, resulting in several new lead compounds at different phases of drug discovery. Surprisingly, these investigations continue to point to cell envelope lipids as *M. tuberculosis*'s Achilles' heels.[7,33,53] They are also prompting the TB field to reconsider previous assumptions that medications targeting the lipid biogenesis of the mycobacterial cell envelope would not have synergistic effects on other drugs, and are not effective on MDR-*M. tuberculosis* isolates.

Current drug discovery attempts have revealed diverse chemotypes that can hinder various components of mycolic acid synthesis, which also have the potential to be developed further. Blocking two systems (the FAS-II and mycolic acid transporter (MmpL3)) seems to be the best appealing target in this pathway for the discovery of anti-TB drugs. Despite their therapeutic potential, lipids associated with TB immunopathogenesis could be useful targets for future preventative approaches, including testing the vaccination potency of CD1-restricted lipid antigens.[54,55] Nonetheless, interest in creating *M. tuberculosis* lipid-based TB serodiagnostics appears to have decreased since previous decades, and significant efforts are now focused on their possibility as biomarkers for tracking TB reactivation, as well as the efficacy of therapies and vaccination.[56,57]

Inhibition of Mycolic Acid Biosynthesis

Alternatives to INH are still under investigation. Freundlich et al introduced a set of 5-substituted triclosan derivatives. Triclosan is an antifungal and antibacterial molecule that can be obtained commercially. These compounds were evaluated against *M. tuberculosis* strains that were resistant to INH, and certain derivatives with aryl and alkyl substituents demonstrated better efficacy than INH.[58] Vilchèze et al[59] screened small compounds' library against the *Plasmodium falciparum* enoyl reductase, which is an InhA ortholog. Considering that INH-resistant strains are caused by mutations in katG, the goal of this screening was to find novel InhA inhibitors which do not need KatG activation. They discovered two compounds (i.e., CD39 and CD117) that had bactericidal efficacy against *M. tuberculosis*. Both molecules were found to be more effective against strains that were resistant to INH. Even in anaerobic environments, CD117 and CD39 suppress mycolic acid biosynthesis and have bactericidal effects.[59]

Inhibition of Mannose-capped Lipoarabinomannan and Phosphatidylinositol Mannoside Biosynthesis

The biosynthetic enzymes of PIM, lipomannan, and ManLAM are promising candidates to invent specific

Table 1. Effect of Agents and Targets in the Mycobacterial Cell Wall Biosynthesis Metabolism

Drug	Target	Effect	References
Caprazamycin	WecA	Arabinogalactan precursor biosynthesis is inhibited.	35-36
Thiacetazone and thiocarlide	InhA protein	Biosynthesis of Mycolic acid is targeted.	37
DPA analogs	AftA,B,C,D	Periplasmic arabinogalactan biosynthesis is inhibited.	38
Ramoplanin	MurG	Mycolic acid biosynthesis is inhibited.	39
Diarylcoumarin	FabD32	Mycolic acid biosynthesis is inhibited.	40
Thiophene compounds	Pks13	Arabinogalactan is inhibited.	41
Tunicamycin	WecA	Arabinogalactan precursor biosynthesis is inhibited.	35
Anthranilic acid analogs	MabA	Mycolic acid biosynthesis is inhibited.	42
Ethylenediamine derivatives			
(I) Ethambutol	Arabinosyltransferase enzymes (encoded by *emb*A and *emb*B genes)	RNA synthesis (arabinogalactan synthesis), namely, cell wall formation is Inhibited.	43
(II) SQ109	MmpL3 and the menaquinone biosynthesis enzymes (*Men*A and *Men*G)	Mycolic acid transport and cell wall biosynthesis are inhibited.	44
Carboxamide derivatives	MmpL3 inhibitors	Cell wall biosynthesis	45-47
Spiropiperidines	MmpL3 inhibitor	Cell wall biosynthesis	45,48
Benzimidazoles	MmpL3 inhibitor	Cell wall biosynthesis	49-50
Pyrrole (BM212)	MmpL3 inhibitor	Direct interaction with MmpL3 and inhibition of MmpL3-mediated trehalose monomycolates transport to affect cell wall biosynthesis	51
Benzothiazinones	Decaprenylphosphoryl-β-D-ribose oxidoreductase (DprE1) inhibitor	Cell wall biosynthesis is inhibited.	52

Note. MmpL3: Mycobacterial membrane protein large 3.

M. tuberculosis drug inhibitors with the ability to synergize or amplify the other drugs' activity when used in combination. Essential characteristics such as the confined distribution of these enzymes to mycobacteria and closely linked actinomycetes, as well as the proven impact on *M. tuberculosis* cell envelope structure and permeability, can aid in finding specifically acting *M. tuberculosis* drug inhibitors. As a result, numerous important enzymes working at different stages of systems (e.g., 'PimA and PimB' at the early stage and late-stage working enzymes including Emb proteins and the other enzymes such as lipid-linked glycosyltransferases which utilize sugars) are being pursued for using target-to-drug techniques. Novel high-throughput screening techniques have been designed for these enzymes.[60] To present, the most effective ManLAM inhibitors are those that target DPA production.

The Role of Mycobacterial Membrane Protein large 3 as a Target for Drug Development Against Tuberculosis

The pathogenesis of *M. tuberculosis* is influenced by the unique architecture of the mycobacterial cell envelope. MmpL3 is a key protein in the biogenesis of the cell envelope in mycobacteria since it is essential for precursor and trehalose monomycolate (TMM) transport.

MmpL3 has become an interesting therapeutic target for various preclinical drugs due to its significance and involvement in TMM transport.[61] MmpL3 transporter activity has recently been reported with a biochemical assay that is spheroplast-based, implying TMM flippase activity. The findings of this study are consistent with genetic analysis studies that show MmpL3 expression is required for *M. tuberculosis* survival. Furthermore, MmpL3 depletion in *Mycobacterium smegmatis* resulted in the buildup of TMMs, as well as a decrease in TDM and mycolyl AG levels.[62] Some compounds have been found to block MmpL3- mediated TMM flipping using the above-mentioned spheroplast-based test. Such MmpL3 inhibitors can be found in a variety of chemical scaffolds which have been proven to have synergistic effects with other antitubercular medications.[51,63] Because of a highly conserved MmpL3 sequence in mycobacteria and corynebacteria, many of these chemical core structures are indeed operative against non-tuberculous mycobacteria such as *Mycobacterium abscessus*, with limited therapies, further raises interest in exploring such a novel pharmacological target.[50,61,64]

SQ109 is a TB medication that has demonstrated encouraging outcomes in phase 2b-3 clinical investigations among MmpL3 inhibitors.[64] It was considered to be safe and have a high tolerance profile in Phase I and Phase IIa clinical trials. This medication was found to have bactericidal action toward *M. tuberculosis* that was multidrug resistant.[65] In a mouse model of TB, it also demonstrated synergistic effects with rifampicin, isoniazid, and bedaquiline, as well as shortened TB clearance. Its mode of action was described as an indirect process that includes proton motive force dissipation.

However, additional research suggests that MmpL3 is really not SQ109's lone target, with other effects such as menaquinone biosynthesis inhibition, which could have similar bacteriostatic effects. MmpL3 is currently the most potential therapeutic target for both TB and non-TB bacteria, and many molecule inhibitors of MmpL3 have been identified. The structural characterization of MmpL3 has recently opened the way to a better understanding of these inhibitors' modes of action, as well as the mechanistic knowledge of MmpL3-dependent TMM transport.[64,65] Novel structural information could be used to rationally improve the lead chemical compounds into extremely effective anti-TB drugs.[66]

Challenges Faced by Agents While Targeting Mycobacterial Membranes

Mycobacterial membranes' selective targeting comes with its own set of obstacles not experienced by the other methods of discovery. Membrane targeting agents for TB face two major obstacles. The first is a knowledge gap about how to structurally modify early hit molecules to increase antimycobacterial efficacy and selectivity. This issue is not unique to mycobacteria, although it may be more severe because the mycobacterial cell membrane is more complicated than that of the other bacteria. The entity's physicochemical property (i.e., cationic amphiphilicity) drives the membrane's attraction.[18,34,67]

The second serious obstacle is that membrane-targeting agents have selective activity. Considering that these drugs are lipophilic, they will very certainly divide mammalian membranes as well and generate harmful off-target effects. Oritavancin, a membrane-disrupting antimicrobial glycopeptide causing mixed-lipid storage abnormalities in both macrophages and fibroblasts, is a good example. Although AMPs may favor bacterial membranes over mammalian membranes, Goldman noted that this might not be the case for membrane-targeting small compounds.[29] The red blood cell hemolysis analysis, which offers a simple yet effective way of eliminating compounds that can harm mammalian membranes, should be used in this respect. For the best leads, *in vivo* acute and chronic toxicity investigations will be necessary.[68]

Despite the challenges, mycobacterial membranes' selective targeting presents an untapped possibility to address associated issues with the existing TB medicines. As greater attention is paid to its therapeutic potential, a deeper knowledge of the science behind the disruptive events will emerge, leading to the development of improved and safer drugs to treat active and dormant TB.[69] Concerns about pharmacological redundancy across pipeline prospects in terms of mechanism of action, symptom profiles, and cross-resistance should be alleviated by the introduction of diverse and new targets.[70]

Strategies for Investigating Novel Tb Antibiotics

There are two techniques to find novel Tb antibiotics, including target- and drug-based types. The drug-based approach uses the investigation of new drug compounds for their potential antimicrobial properties against *M. tuberculosis*. During this process, different related chemical compounds are screened for their antimicrobial activity against *M. tuberculosis* to discover novel antibiotics for the treatment of *M. tuberculosis*-related infections. A 'prodrug platform' can be used to screen potentially ideal antibiotics for their killing activity against bacterial cells, as well as persisters. During this approach, the drug compound is delivered to bacterial cells to be activated by bacterial enzymes through drug-target interactions, and the compound's covalent binding with unrelated targets is expected to happen during this process. The killing concentration of the 'hit' molecule is decided after the chemical library screening of the desired drug molecule. By assessing bacterial cell growth, this approach finds out a good range of antibacterial activities, along with good bacterial penetration properties of a compound, and target sensitivity by understanding target-ligand binding characteristics. It also helps avoid an issue of '*MDR efflux*'.[71,72]

The *M. tuberculosis* genome sequencing and thousands of additional potential therapeutic targets' annotation made target-based drug development possible. In a target-based strategy, a therapeutic target is chosen, purified, and explored to find small molecules that influence *in vitro* target function by using inhibitory assessment. Target-driven techniques have the advantage of being able to appropriately prioritize new targets based on appealing traits; for example, new targets without drug resistance have an exploitable active site structurally, and their extracellular surface presence promotes antibiotic access and a variety of other factors.

While target-based techniques have significantly improved treatment capabilities against several viral diseases and cancers, the outcomes for antibacterial activities have been disappointing.[73] Target-based techniques have failed to yield a single novel medication for TB treatment. Although there are many reasons for target-based techniques' failure, during the screening of libraries for drug-like small molecules, there is a lack of chemical diversity and penetration ability into bacterial cell walls, preventing xenobiotic metabolism.[64,74]

Due to the drawbacks of such target-based techniques, drug discovery in the TB field has mostly returned to phenotypic screening. From streptomycin's identification in 1944 until the bedaquiline approval in 2012, these phenotypic screens have been exceedingly successful, delivering all the drugs now used to cure TB. However, phenotypic screenings have their own set of limitations, including the frequent rediscovery of compounds targeting a limited set of pathways and

so-called "promiscuous" *M. tuberculosis* targets such as *mmpL3* and *dprE1*. In addition, the molecular target and mechanism of action (MOA) should be discovered for hit compounds to proceed, and finding MOA is typically difficult. Moreover, the variations between *in vitro* growth settings and those observed during *in vivo* infection can lead to the discovery of powerful *in vitro* growth inhibiting factors having MOAs that are unnecessary during infection.[73-75]

Considering the limitations of target- and small-molecule-centric techniques, ongoing TB antibiotic research activities will keep relying on a combination of the two. Target-based techniques have the potential to enhance drug target space to add the greatest biologically appealing targets, but they have a high rate of target attrition. Whole-cell phenotypic assays can be effective, but they typically suffer from a limited target space and insufficient information of hit MOA up front. There are several chances to enhance TB antibiotic discovery, including chemical, bioinformatic, and technological advances.[76]

Consideration for Developing Novel Anti-tubercular Agents

For an effective anti-tubercular treatment strategy, these compounds should be ideally inexpensive and compatible with combinational therapy, shorten treatment time, and have a minimal mutation resistance frequency.[77] They must also have low toxicity over extended periods of time with few side effects.[78] In addition to these beneficial traits, finding new hits and leads for *M. tuberculosis* itself is a difficult task. The growth rate of *M. tuberculosis* is slow, which has a negative impact on research progress. Drugs targeting *M. tuberculosis* must be effective at different stages of infection since *M. tuberculosis* can survive in a variety of microenvironments.[79] Since the last decades, advances in molecular and genomic techniques, including important insights obtained from whole genome sequencing,[11] have shed more light on *M. tuberculosis*'s biochemistry and biological characteristics involved in their pathogenicity. This has allowed for the development of novel chemotherapeutic agents that target newly discovered cellular processes.[80]

Conclusion

Despite the availability of efficient treatment regimens, there is a worldwide search for novel anti-tubercular drugs to combat the growing threat of drug resistance, as well as to shorten the length of chemotherapy and reduce any associated toxicity. The rise of antibiotic-resistant pathogenic bacterial strains necessitates the hunt for novel medications to combat infectious diseases. In accordance with this urgency, lots of new studies have been published in the last decade aimed at identifying novel chemical scaffolds and new targets for anti-TB drug development. To this purpose, disrupting the biogenesis of mycobacterial cell envelope holds extensive potential for new drug development. The identification of a number of new chemical scaffolds inhibits different stages of lipid synthesis, including the synthesis of mycolic acids and ManLAM. MmpL3 inhibition, which is responsible for mycolic acid transport, is a promising technique that has the ability to mimic isoniazid efficiency without the development of mycobacteria resistance against it. MmpL3 is currently one of the most favorable therapeutic targets for anti-TB drugs. Despite these recent developments, a clear mechanism describing MmpL3-mediated TMM transport regulation remains elusive, as does the action of MmpL3 inhibitors. Thus, more research is needed in the future to understand the potential interaction of MmpL3 with the other cell envelope components and the functional importance of these related interactions. Understanding the mechanisms of such related interactions, biosynthesis, and the like could pave the way for exploring new ways to battle drug-resistant *M. tuberculosis* strains and enhance the existing treatment protocols.

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Competing Interests

There is no conflict of interests.

Ethical Approval

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