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Letter to the Editor

Exploring the potential of multi-target-directed ligands for tuberculosis treatment

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Dear Editor,

Tuberculosis (TB) is a major public health problem worldwide, with an estimated 10 million new cases and 1.4 million deaths annually. Despite the availability of effective antibiotics, the emergence of drug-resistant strains of the bacterium poses a significant challenge to TB control efforts.[1] Therefore, there is an urgent need for the development of new and effective drugs to combat this deadly disease. Multi-target-directed ligands (MTDLs) are a promising approach for the treatment of TB. MTDLs are small molecules that have the ability to bind to multiple targets simultaneously, thereby providing a more comprehensive approach to drug therapy. Traditional drugs target a single receptor or enzyme, which can lead to the development of drug resistance as the bacterium adapts to the selective pressure. In contrast, MTDLs can target multiple pathways and mechanisms of action, making it difficult for the bacterium to develop resistance.[2]

There are several drugs that have been identified to target multiple drug-binding sites against TB (Table 1), and one of them is SQ109.[3] SQ109 and its derivatives are a class of antitubercular drugs that exhibit multi-target properties. They have been found to target several transport proteins, such as MmpL3 and MmpL11, which are involved in the biosynthesis of the mycobacterial cell wall, and enzymes, such as MenA and MenG, that are involved in the biosynthesis of menaquinone.[3] TB47 is another MTDL that works by targeting the respiratory cytochrome bcc complex, which is involved in the electron transport chain of mycobacteria.[4] TB47 binds to the Qo site of the cytochrome bcc complex, thereby inhibiting the electron transport chain, leading to the disruption of the mycobacterial membrane potential and ultimately the death of the bacteria. In addition, TB47 has been found to inhibit the biosynthesis of mycobacterial cell wall components, such as arabinogalactan and mycolic acids, which are crucial for the integrity and survival of the bacteria.[4] By targeting multiple pathways, TB47 exhibits the potential to overcome drug resistance and enhance the effectiveness of TB treatment. Pretomanid is another example of a MTDL drug used to treat TB which was recently approved by the Food and Drug Administration (FDA).[5] The BPaL regimen comprises three drugs: Bedaquiline, Pretomanid, and Linezolid, which work through different mechanisms to target multiple pathways in *Mycobacterium tuberculosis* (Mtb).[5] Bedaquiline inhibits the mycobacterial adenosine triphosphate (ATP) synthase, while Pretomanid targets the type II fatty acid synthase system, and Linezolid inhibits protein synthesis. The combination of these drugs in the BPaL regimen has been shown to be effective in treating drug-resistant TB, including extensively drug-resistant TB, indicating the potential of MTDLs in TB treatment.[5]

MTDLs in TB treatment exert their pharmacodynamics through a multifaceted mechanism of action. These ligands are engineered to interact with multiple targets within Mtb, disrupting essential biological processes crucial for bacterial survival and replication. By simultaneously targeting various pathways, such as cell wall synthesis, protein synthesis, DNA replication, and metabolic pathways, MTDLs enhance the efficacy of treatment. This multi-target approach helps minimize the development of drug resistance by reducing the bacterium's ability to adapt through single-point mutations. Moreover, the use of MTDLs has the potential to lower the required dosage of individual drugs, reducing the risk of adverse effects and enhancing treatment outcomes.[6,7] The pharmacokinetics of MTDLs in TB treatment are influenced by factors, such as their chemical properties. These ligands undergo processes of absorption, distribution, metabolism, and excretion (ADME), which are crucial

Table 1. Multi-target directed ligands (MTDLs) for the treatment of tuberculosis.

Drug	Target	Mechanism of action
SQ109	MmpL3, MmpL11, MenA, MenG	Inhibits the biosynthesis of the mycobacterial cell wall and menaquinone
TB47	Cytochrome bcc complex	Inhibits the electron transport chain, disrupts the mycobacterial membrane potential, and kills the bacteria
Pretomanid	Type II fatty acid synthase system	Inhibits the synthesis of mycobacterial cell wall components
Bedaquiline	ATP synthase	Inhibits the mycobacterial ATP synthase
Linezolid	Protein synthesis	Inhibits protein synthesis

for their therapeutic effectiveness. Factors such as molecular weight, lipophilicity, and solubility play a role in determining their absorption and distribution within the body. Metabolic stability is important to ensure that MTDLs are not rapidly metabolized, allowing for sustained therapeutic exposure. Rational chemical modifications can be employed to enhance their metabolic stability and prolong their half-life. In addition, it is important to consider potential drug–drug interactions with other anti-TB drugs, as these interactions can impact the pharmacokinetic profiles of MTDLs, potentially affecting their efficacy and safety.[6,7]

In vitro models serve as valuable tools for assessing the antimicrobial activity of MTDLs against Mtb, including drug-resistant strains. These models involve culturing Mtb with MTDLs to measure their inhibitory effects on bacterial growth. Cytotoxicity and host cell penetration can be evaluated using macrophage cell lines. Animal models, such as mice and guinea pigs, are commonly used for preclinical evaluation. Mouse models, such as C3HeB/FeJ or BALB/c, allow assessment of MTDL efficacy by measuring bacterial burden in the lungs and other organs, and evaluating histopathological changes.[8] Guinea pig models resemble human TB pathology and assess drug regimens for active and latent TB.[9] Pharmacokinetic studies in animals provide insights into ADME of MTDLs, aiding in dosing optimization. Animal models are also used to evaluate safety and toxicity profiles through acute and chronic toxicity studies and organ-specific evaluations. Consideration of model relevance to human TB pathology and complementary *in vitro* studies with human-derived cells is essential.

MTDLs offer potential advantages in TB treatment, including overcoming drug resistance, targeting multiple pathways, and enhancing efficacy. However, challenges exist in identifying suitable targets and optimizing pharmacokinetic properties. Target selection must consider TB's complexity, and optimizing solubility, stability, and bioavailability is crucial. These challenges need to be addressed to harness the full potential of MTDLs for effective and safe TB treatment.

In conclusion, MTDLs are a promising approach for the treatment of TB. They have the potential to overcome the problem of drug resistance and provide a more comprehensive approach to drug therapy. The development of MTDLs for TB treatment is still in the early stages, but there are several promising compounds that have been reported in the literature. Further research is needed to identify suitable targets for MTDLs and optimize their pharmacokinetic properties. With continued research and development, MTDLs have the potential to make a significant contribution to the fight against TB.

Declarations

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Consent for publication
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