

EMERGING DRUG TARGETS FOR TUBERCULOSIST. Rajathilagam¹,¹Assistant Professor, Department of Pharmacology, ESIC Medical College, K. K. Nagar, Chennai**ABSTRACT****BACKGROUND**

The goal of Tuberculosis (TB) drug discovery and development is to achieve TB drugs and drug regimens that are well understood and superior to those available today in their efficacy, speed of action, safety and tolerability, ease of use for all patient populations and accessibility. Strategies recently used in TB drug development include re-evaluation of existing TB drugs to optimise their utility; repurposing of drugs registered for non-TB indications as components of TB drug combinations; development of improved analogs of compounds or drugs with some known but limited value for TB and development of novel chemical entities with new modes of action against TB. The emerging drug targets for TB are targeting Mtb Iron Acquisition and Storage, MmpL, Cholesterol Metabolism, Targeting Energy Generation: Inhibitors of the Respiratory Chain and ATP Synthesis and cytochromes. Such vulnerable pathways and processes might provide a path toward safer, novel regimens for TB with greater treatment-shortening potential.

KEYWORDS

Tuberculosis, Drug Targets, Drug Regimens, Novel Mechanism.

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BACKGROUND

The goal of Tuberculosis (TB) drug discovery and development is to achieve TB drugs and drug regimens that are well understood and superior to those available today in their efficacy, speed of action, safety and tolerability, ease of use for all patient populations and accessibility.^[1]

New agents would ideally have the following attributes: a novel mechanism of action to attenuate cross-resistance; rapid bactericidal activity to reduce duration of therapy; optimised pharmacokinetic/pharmacodynamic (PK/PD) properties for once-daily oral administration, low potential for drug-drug interactions to allow combination therapy, especially with other TB drugs and current HIV therapeutics and excellent safety profile to allow for use in children and pregnant women. These ideal criteria are coupled with other practical goals such as inexpensive manufacturing, high compound stability, narrow spectrum of activity, high tolerability and a low rate of spontaneous resistance emergence.^[2]

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The current global TB drug development pipeline includes four compounds under evaluation for active pulmonary TB in phase III clinical trials. Two of these four compounds, the fluoroquinolones, moxifloxacin and gatifloxacin, are being investigated as part of 4-month regimens, combined with first-line TB drugs for drug-sensitive TB.

The other two, bedaquiline (diarylquinoline) and delamanid (nitroimidazole) are being evaluated as additions to background therapy for MDR-TB. Another nitroimidazole, PA-824 is poised to enter Phase III clinical trials as part of a novel drug combination with moxifloxacin and pyrazinamide, in which it will be evaluated as a 4-month regimen against drug-sensitive TB and as a 4- or 6-month regimen against MDR-TB.^[1]

The best-validated Mtb drug targets are ATP synthesis and PMF (Proton Motive Force) generation owing to the clinical successes of the ATP synthase inhibitor TMC-207 (Bedaquiline) and the cornerstone TB drug Pyrazinamide, which disrupts the PMF.^[1] This article has analysed and summarised the other postulated drug targets for Mtb.

Emerging Drug Targets Targeting Mtb Iron Acquisition and Storage

Iron is an essential nutrient for all living organisms including pathogenic bacteria in an infection. During infection, Mtb localises inside host macrophages where it has access to transferrin-bound iron. Mtb secretes two classes of siderophores, mycobactins and carboxymycobactins to bind iron, obstructing it from the mammalian iron binding proteins and then internalises the iron laden siderophores through its receptors. Novel drugs targeting inactivation of siderophore export and recycling would deliver a one-two punch to Mtb by reducing its capacity to take up iron.

Although, iron acquisition is required for the growth and virulence of Mtb, it seems that proper iron storage within the pathogen is just as crucial. Various investigators have targeted siderophores for the development of novel TB drugs. One approach has been to develop agents that directly inhibit enzymes involved in siderophore synthesis. Another approach targets the iron-dependent regulator protein (IdeR) that represses siderophore synthesis genes and virulence factors when sustainable iron levels have been achieved.^[1] The biosynthesis, transport and utilisation of siderophores are potential targets for Mtb drug discovery, as Mtb survival and virulence seem to be directly related to iron availability.

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Targeting MmpL

MmpLs (Mycobacterial membrane protein large) are membrane proteins and may thus be more accessible for targeting than cytosolic enzymes. Various studies clearly indicate the importance of this protein family for growth, transport of vital cell wall components with some involvement in virulence and perhaps the efflux of small molecules that are toxic to the bacterial cell.^[1] It is therefore interesting to imagine a single molecule that might inhibit a variety of MmpL proteins and potentially affect growth, virulence and sensitivity to other drugs.

Targeting Cholesterol Metabolism

Mounting evidence^[3,4,5,6] suggests that Mtb uses the host's cholesterol as a source of carbon and energy during infection. From experimental data by Senaratne et al 2008, it seems that although cholesterol catabolism by Mtb is important during infection, if ineffectively metabolised cholesterol may be toxic to the pathogen. Importantly, both phenomena can be exploited for TB drug discovery, for drugs that inhibit cholesterol metabolism or those that inhibit enzymes, which remove the toxic intermediates of cholesterol metabolism.

Targeting Cytochromes

QcrB (Cytochrome bc₁) is an emerging and highly vulnerable drug target of Mtb. An essential respiratory chain component, cytochrome bc₁ (complex III) is required for ATP production. Consistent with QcrB inhibition, there is massive and rapid ATP depletion in treated Mtb. Lansoprazole belongs to a class of drugs known as "proton-pump inhibitors" that prevent heartburn and ulcers. Being highly active against drug-resistant strains of Mtb, by inhibiting QcrB this novel class of drugs provides us with an excellent opportunity to treat tuberculosis.^[7]

Other emerging drug targets are the Mtb ClpP Protease, Central Carbon Metabolism and ROS and NOS Generation.

A robust global TB drug discovery portfolio is crucial to achieving the goal of new, simpler, shorter and better TB drug regimens useful for all patient populations. Thus, the current global pipeline suggests a few solutions that could be used to improve the situation and produce better, more easily developable leads. Such vulnerable pathways and processes might provide a path toward safer, novel regimens for TB with greater treatment-shortening potential.

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