

# Targeted Therapies- A Promising Cure For TB, the Leading Deadliest Infectious Disease Worldwide

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## Abstract

We all know how COVID-19 took the world by a storm, but there has been an old but consistent contender that has now even surpassed COVID-19 to claim the title of Deadliest infectious disease. This is none other than our very well known Tuberculosis which is caused by *Mycobacterium tuberculosis*.

Though TB is curable with standard course of antibiotics there is still a rising need for targeted therapies in order to reduce the risk the mortality rate. This article discusses about the different targeted therapies that could possibly be more effective than the traditional treatment methods.

**Keywords:** Tuberculosis, Doxycycline

*Abbreviations:* TB- Tuberculosis, MMP- Matrix Metalloproteinase, miRs- Micro RNAs, HDT- Host Directed Therapy, VEGF- Vascular Endothelial Growth Factor, PDE- Phosphodiesterase, MDR TB - Multi drug resistant Tuberculosis, XDR TB- Extra drug resistant tuberculosis

## Introduction

TB is one of the prevalent and severe infectious diseases worldwide. An estimate conducted in 2019 revealed that 10 million people developed active TB leading to 1.6 million deaths. [1] Although there had been a standard cure for this disease, it fails to work effectively against the newer forms of TB like MDR TB and XDR TB. *Mycobacterium tuberculosis* the causative agent of TB leads to a granulomatous inflammation which contains bacilli at the site of infection. This triggers an aggressive humoral and cellular immune response that could actually result in an unfavorable inflammation leading to extensive irreversible host tissue damage which is seen as lesion necrosis and cavitation. [2]

Thus host directed therapies that target this granulomatous formation should prove to be highly effective in treating the disease. This article discusses the latest improvements in this regard.

## Methods

1) Doxycycline inhibits MMP activity leading to inhibition of cavity formation

One of the serious complications of TB is Cavity formation. Recent studies have shown the effectiveness of Doxycycline at limiting collagen destruction by inhibiting the M. tuberculosis-mediated neutrophil-derived nuclear factor-kappa B (NF-kB)-dependent MMP-8. There has also been a rise of neutrophil extracellular traps holding the MMP-8 from TB samples.

## 2) PAZOPANIB - Targeting Granuloma associated angiogenesis

The typical host response following aerosol exposure of TB is Infiltration granuloma formation by alveolar macrophages. The Anti-tubercular drugs that are traditionally used are unable to attain an effective therapeutic concentration within the granulomatous lesion VEGF has been noted to increase vascular permeability and angiogenesis. Certain clinical trials have shown that the drug, Pazopanib which is a VEGF receptor tyrosine kinase inhibitor to be a potential therapy targeting granuloma angiogenesis by inhibiting development of caseous necrosis.

## 3) MicroRNAs - Regulators Of Gene expression

miRs mediated inflammation & immune response in TB.

Thus by using miR mimics to increase miR levels or anti-miRs to decrease harmful miRs, we can regulate the host's immune response. Though this method has not yet been implemented into real life practice, the clinical trials using delivery methods such as lentiviral vectors or nanotechnology based carriers in animal models have shown to be very promising in the prognosis of future TB treatments.

## 4) Therapies targeted at inducing autophagy

Clinical trials have shown Vitamin D & Interferon-gamma to boost lysosomal fusion with phagosomes containing M. tuberculosis. Vitamin D as a dietary supplement has not shown to be that effective in TB treatment. However, they cannot be ruled out completely.

Nitazoxanide, a niclosamide derivative has been shown to be a potent inducer of autophagy. These used in combination with existing Anti-TB drugs have shown to be more effective.[1][4]

## 5) Corticosteroids

Research has shown that 17% of TB-associated mortality can be reduced with the use of Corticosteroids. Dexamethasone has shown to significantly reduce cytokine response to TB antigens.

## 6) Pro-angiogenic host targeted therapy

Studies have shown that increased levels of VEGF will increase blood supply & angiogenesis leading to better drug penetration & increase the access for host immune cells to reach granuloma.

## 7) Thalidomide - adjunctive therapy for TB meningitis

Clinical paediatric trials have shown thalidomide limiting TNF production by modulating cAMP levels which is regulated by host phosphodiesterase. PDE4 inhibitor CC-3052, a thalidomide analog when used in a mouse model increased isoniazid effectiveness by reduced TNF production. However, teratogenic properties of thalidomide makes it questionable for its implementation in the treatment of TB.

#### 8) Imatinib - ABL inhibition

Use of Imatinib mesylate, an ABL tyrosine kinase inhibitor resulted in increase in killing and promoted acidification of mycobacterial phagosome. When co-administered with first line drugs it was shown to produce a synergistic effect. [4]

#### 9) Protein kinase - Host protein Target

The absence of an enzyme, Double stranded RNA-dependent protein kinase in mice resulted in better control of bacterial burden. Thus by targeting these specific host proteins, the overall burden of TB is reduced. Though this principle has not been implemented in human trials, the results seem to be promising. [5]

#### 10) Collapse therapy

A surgical modality that has been used against preventive the spread of TB is surgical lobectomy. Other methods include pneumothorax, pneumoperitoneum, phrenic crust, thoracoplasty, extrapleural lucite pack. These methods were based on the principle that when we collapse the lung and its associated cavitory lesions, more normal tissue margins become closely opposed. This leads to the reestablishment of blood supply which in turn promotes wound healing and resolution. Removing the lung lobes also physically reduces the bacterial and lesion burden of the host.

Patients especially with MDR and XDR who fail to respond to the traditional treatment can benefit with this surgery. [4][7]

### **Conclusion**

The conventional treatments that have been used time and time again for the treatment of TB may have been effective in the previous years but with rise of multiple drug resistant strains, these have proven to become less effective leading to the mortality rate. Thus there is a definite need in newer methods in order to tackle the current scenario. With this article we are aware of methods such as Doxycycline, Pazopanib, miRs, Imatinib, corticosteroids, thalidomide & more that have proven to be more effective against these newer strains of TB. The future treatment methods of TB seem to be very promising & so there must be a more wider approach in conducting clinical trials before they can be established as standard courses of treatments against this deadly disease.

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