Introduction

The pathogen *Mycobacterium tuberculosis* represents a deadly threat to the worldwide population, especially poor and developing countries, as it kills approximately 2 million people each year according to the World Health Organization. Although it can affect any part of the body, *M. tuberculosis* most often infects the lungs and is transmitted in tiny droplets released into the air by coughing and sneezing.

In recent years, the effectiveness of many antibiotics used to treat tuberculosis has decreased as multi-drug resistant strains of tuberculosis have been identified in over 100 countries, so patients with active tuberculosis infections must take a myriad of drugs to prevent the bacteria from developing further resistance. Because of overuse and increasing resistance to current antibiotics, researchers are working to develop new drugs to more effectively treat tuberculosis.

![Figure 1: Symptoms, transmission, and diagnosis of tuberculosis](image1.png)

![Figure 2: Healthy lungs vs. tuberculosis-infected lungs](image2.png)

When cellular leucine levels are low, the *M. tuberculosis* enzyme alpha-isopropylmalate synthase (IPMS) catalyzes the condensation of acetyl-CoA with alpha-ketoglutarate (alpha-KIV), the first step in the production of the essential amino acid, leucine. As leucine levels increase in the organism, leucine biosynthesis is shut down by its binding to an allosteric site in the C-terminal domain of IPMS, which inhibits the production of additional leucine. Researchers are working to design a competitive inhibitor that would bind at the allosteric leucine binding site and shut down the pathway, thus depriving *M. tuberculosis* of this essential amino acid. The development of new drugs specific to *M. tuberculosis* offers a promising way to overcome the problem of antibiotic resistance and offers new tools to reduce life-threatening tuberculosis infections.

![Figure 3: Prevalence of multidrug resistance in M. tuberculosis](image3.png)

![Figure 4: Leucine biosynthetic pathway in M. tuberculosis](image4.png)

![Figure 5: Hydrogen – Deuterium exchange in one monomer of IPMS](image5.png)

Potential Solution to *Mycobacterium* Infection

The growing issue of antibiotic resistant bacteria has become increasingly difficult to treat. Tuberculosis is one of the diseases that has been plagued by this growing issue. Cutting off the essential leucine biosynthetic pathway offers a new possibility to cure people who contract multidrug resistant tuberculosis. This strategy has the potential to enhance or replace existing antibiotics targeting *M. tuberculosis*. By inhibiting either the active site in the catalytic domain or activating the allosteric site in the C-terminal domain, scientists would be able to shut off the biosynthetic pathway for leucine, thus, preventing *Mycobacterium tuberculosis* from surviving in the body.

The leucine biosynthetic pathway begins when IPMS catalyzes a reaction between Acetyl-CoA, Zn²⁺, and alpha-KIV, acetyl-CoA, and Zn²⁺. Leucine will bind to the enzyme to inhibit the production of additional leucine, which can be taken advantage of in drug development. Researchers would like to design a competitive inhibitor that would interact at the leucine allosteric binding site which offers a potent and specific way to shut down the pathway.

![IPMS Molecular Structure](image6.png)

![Map of areas affected by TB](image7.png)

![Prevalence of TB cases](image8.png)

![TB cases by age and sex in the U.S.](image9.png)

When a country is shaded darker, there is a higher incidence of TB in that location. The nations with the highest incidences of TB are often the most underdeveloped.

This graph demonstrates that while the number of TB cases among US-born people (represented by blue bars) have decreased consistently over the last fourteen years, cases of TB among foreign-born persons have remained fairly constant (represented by gray bars).

This bar graph illustrates the incidence of tuberculosis by age group and gender in the U.S. As shown by the graph, the 65 + age group has the highest incidence of TB.

![Figure 6: Symptoms, transmission, and diagnosis of tuberculosis](image10.png)

![Figure 7: Healthy lungs vs. tuberculosis-infected lungs](image11.png)

References


