21st Century Drug Design
Blocking Prokaryotic Cell Wall Synthesis By Stopping DHPR

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Abstract
The bacteria Mycobacterium tuberculosis is the causative agent for tuberculosis (TB) and has been present since at least 2400 BCE. Two million people worldwide die from TB annually, with the highest death rates in developing countries. This resurgence of TB can be attributed to many factors, one of which is the bacteria’s increasing resistance to a broad spectrum of antibiotics. In TB, antibiotics act to cause leakage in the prokaryotic cell wall, which leads to cell death. Resistant bacteria have acquired mutations in key enzymes involved in cell wall formation, thus preventing antibiotics from inducing wall leakage. Therefore, a need exists for development of new types of drugs to inhibit or kill infectious bacteria. One new path involves targeting an enzyme, Dihydropyrimidine reductase (DHPR), which is used to produce prokaryotic cell walls. When this enzyme is inhibited, the cell wall of M. tuberculosis becomes unstable, killing the bacterium. DHPR catalyzes a chemical reaction in the metabolic pathway leading to dianaminoplate, an essential cell wall component. If DHPR can be inhibited by a substrate competitor, then a potential drug lead may be identified. Understanding how the enzyme’s active sites function will facilitate the optimization of a recently designed inhibitor of DHPR. Specifically, the research will explain how this molecule may interact with the 4 binding pockets on DHPR. For this drug to work, is binding required at 1, 2, 3, or all 4 pockets, and why? Does binding at one pocket affect what goes on at the other 3? These questions need to be answered before a drug molecule can be rationally engineered against DHPR.

Drug Design
1. Metabolic pathway selection: unique to pathogen
2. Enzyme selection: no interference with the patient’s metabolism
3. Drug affinity testing: preferential binding at the active site
4. Model organism lab tests
5. Clinical trials

How does the designer drug bind to DHPR?
Two models of enzyme-substrate binding

MCW model: substrate binding to one monomer affects all tetramer conformations simultaneously

KNF model: substrate affects monomers sequentially

We have not yet discovered which model DHPR follows, or how it would affect our prospective drug design

A Timeline of TB

First TB antibiotic developed by Waksman, but is too toxic for use - 1940
TB found in Egypt 2400 BCE
An estimated 2 million people die annually from TB; death rates are highest in developing countries.
Development of a drug that can inhibit DHPR can circumvent the issues of XDR-TB, reducing death rates dramatically.

Past
Robert Koch isolates TB bacteria - 1882
New antibiotics for TB become more prevalent and safer to use - 1945-1960

Present

Future
Healthy lung - no TB bacteria present

Multi-drug resistance (XDR-TB) has become a significant issue, currently most prevalent in Europe.

M. tuberculosis bacteria in a lung

Symptoms of TB
-Coughing up blood
-Chest pain
-Uncontrollable coughing
-Fever
-Chills
-Fatigue
-Weight loss

Treatment of TB
Current antibiotics used:
-Isoniazid
-Rifampicin
-Ethambutol
-Pyrazinamide

When TB becomes active in a previously treated patient the bacteria is often drug resistant.