CALIFORNIA STATE SCIENCE FAIR
2004 PROJECT SUMMARY

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Project Title
A Structural Genomic Approach to Mycobacterial Drug Design Targeting Replicative Synthesis: Structure & Function of dnaQ

Abstract

Objectives/Goals
Multidrug resistant tuberculosis has emerged as a major public health threat; thus, new strategies are needed for mycobacterial drug development. The ultimate goal of this ongoing study is to design a drug to inhibit the function of a protein important for survival of the tuberculosis bacterium from the M. tuberculosis H37Rv genome. The present study focuses on determining and validating the structure of a protein target and conducting a preliminary virtual ligand screening of potential compounds for the design of a putative drug.

Methods/Materials
Genes from the H37Rv genome were selected as encoding potential protein drug targets, based upon annotation, sequence and fold similarity, and literature search, and then prioritized. Valid homology models were produced for high priority targets and functionally analyzed. A preliminary library of compounds was screened in silico for binding to the targets.
Materials included the sequenced genomes for laboratory and clinical strains of Mycobacterium tuberculosis, H37Rv and CDC1551, Swiss Institute for Bioinformatics proteomics tools; homology modeling, structure validation, and virtual ligand screening software including LOOPP, 3D-PSSM, Domain Fishing, RAMPAGE, Swiss Model, Deep view, ICM-Pro.

Results
Thousands of genes were examined, and dnaQ (Rv3711c) was given the highest priority among these genes for modeling and virtual ligand screening. dnaQ, encoding the epsilon subunit of the DNA polymerase III core, serves as the proofreader in the replicative synthesis of the bacterial DNA, affecting organism viability. The model of dnaQ is comprised of two domains: an N-terminal catalytic exonuclease domain, and a previously unknown C-terminal BRCT-like domain. Virtual ligand screening results suggest that carbonyldiphosphonate derivatives are promising drug lead compounds.

Conclusions/Discussion
dnaQ is a valid and promising antimycobacterial drug target. Because it is responsible for proofreading base-pair mismatches in the replicative synthesis of bacterial DNA, inhibition of dnaQ catalytic activity will affect organism viability. A valid homology model of dnaQ has been produced and a family of promising lead compounds was discovered for drug development. Future research will include the validation of native and complexed structures of the target by crystallography, followed by in vitro and in vivo assays of inhibition by proposed drug lead compounds.

Summary Statement
The two-domain structure of dnaQ was modeled in silico, validated, and analyzed; a family of potential lead compounds was discovered for the design of a drug for dnaQ.

Help Received
Used lab equipment at California State University, Fullerton under my mentor, Dr. Katherine Kantardjieff; my school counselor, Ms. Cheney, provided encouragement and support