SMART Teams 2015-2016 Research and Design Phase

Divine Savior Holy Angels SMART Team

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Mycobacterium Delirium: Inhibiting Leucine Biosynthesis to Starve M. tuberculosis

PDB: 40V4

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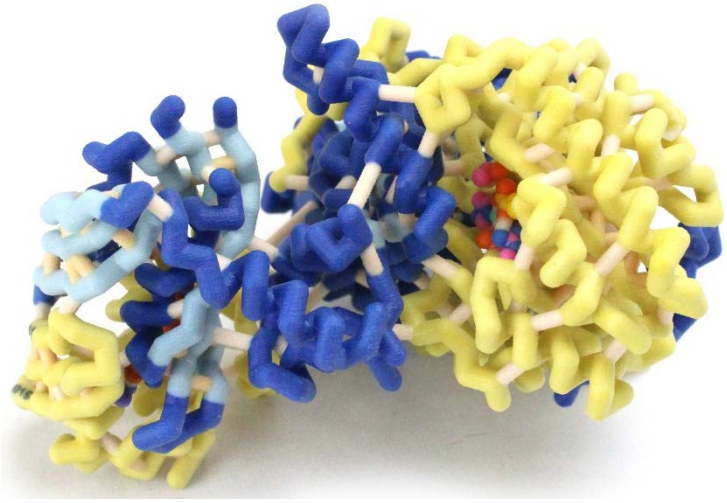
Koon, N., C. J. Squire, and E. N. Baker. "Crystal Structure of LeuA from Mycobacterium Tuberculosis, a Key Enzyme in Leucine Biosynthesis." Proceedings of the National Academy of Sciences 101.22 (2004): 8295-300. Print.



Format: Alpha carbon backbone
RP: Zcorp with plaster

Description:
The pathogen *Mycobacterium tuberculosis* represents a deadly threat to the worldwide population, especially poor, developing countries, as it kills approximately 2 million people each year according to the World Health Organization. Because of overuse and increasing resistance to current antibiotics, researchers are working to develop new drugs to more effectively treat tuberculosis. *M. tuberculosis* alpha-isopropylmalate synthase (IPMS) is a bacterial enzyme that catalyzes the production of leucine, an essential amino acid. When cellular leucine levels are low, the biosynthetic pathway of leucine is initiated by IPMS when three ligands; alpha-ketoisovaleric acid (alpha-KIV), acetyl-CoA which is not included in our model, and Zn^{2+} interact at IPMS's active site. IPMS has two distinct structural domains: an N-terminal alpha/beta catalytic domain which includes the active site and a C-terminal regulatory domain that includes the leucine binding site. As leucine levels increase in the organism, its biosynthetic pathway is shut down by leucine binding to an allosteric site in the C-terminal domain of IPMS which inhibits the further production of additional leucine. The protein amino acids tyr554 and ala536 play a role in the interaction with the leucine ligand. The protein amino acids arg80, asp81, his287, his285, and thr254 interact with the alpha KIV. These interactions allow for the production of leucine through the initiation of the biosynthetic pathway of leucine catalyzed by IPMS. Researchers are working to design a competitive inhibitor that would interact at the allosteric leucine binding site and shut down the pathway, thus depriving *M. tuberculosis* of this essential amino acid. Without the ligands leucine, Zn^{2+}, and KIV the tuberculosis bacteria would die. The Divine Savior Holy Angel High School SMART (Students Modeling A Research Topic) Team modeled IPMS using 3D printing technology to investigate IPMS catalysis and feedback inhibition within the leucine biosynthetic pathway. 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.

Specific Model Information:

- Catalytic domain (B) are highlighted medium blue.
- Regulatory domain (A) are highlighted khaki.
- Struts are colored misty rose.
- Hbonds are colored navajo white.
- Beta sheets in the catalytic domain are highlighted light steel blue.
- Zinc is highlighted in turquoise.
- Alpha-ketoisovaleric acid (alpha-KIV) is displayed in ball and stick with oxygen and nitrogen atoms highlighted in cpk and carbon atoms highlighted in gold.
- The leucine ligand is displayed in ball and stick with oxygen and nitrogen atoms highlighted in cpk and carbon atoms highlighted in pink.
- The amino acids tyr554 and ala536 (displayed in ball and stick with oxygen and nitrogen atoms highlighted in cpk, and carbon atoms highlighted in dark orchid) interact with leucine.
- The amino acids arg80, asp81, his287, his285, and thr254 (displayed in ball and stick with oxygen and nitrogen atoms highlighted in cpk, and carbon atoms highlighted in fuschsia) interact with alpha KIV.
- Acetyl coenzyme A molecule (displayed in ball and stick and colored cpk) interacts in the catalytic domain

http://cbm.msoe.edu/smartTeams/index.php

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