

Saint Joan Antida SMART Team

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Is it possible to find a cure for cancer?

PDB: 4JX5

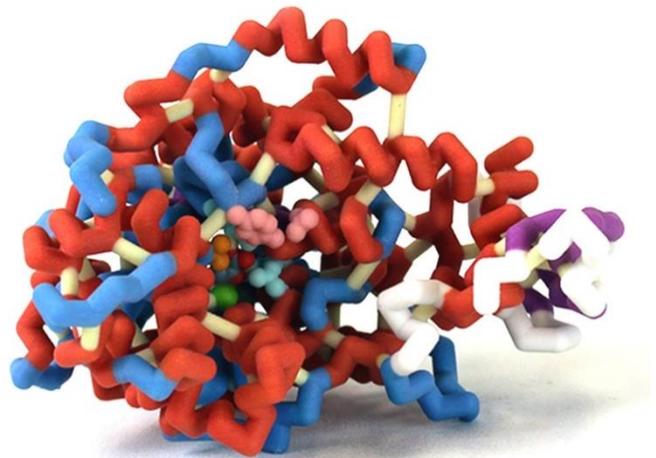
Primary Citation: Lietzan, A.D., St Maurice, M. (2013). A Substrate-induced Biotin Binding Pocket in the Carboxyltransferase Domain of Pyruvate Carboxylase. *Journal of Biological Chemistry* 288: 19915-19925.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Inhibiting pyruvate carboxylase could lead to future treatments for cancer by preventing cancer cells from multiplying. Pyruvate carboxylase is an enzyme found in the mitochondria of animal cells and contributes to the mitochondrial tricarboxylic acid (TCA) cycle by converting pyruvate into oxaloacetate that the cycle needs to generate precursors used to make lipids, amino acids, and nucleotides. Cancer cells rely heavily on many of these precursors to divide. Pyruvate carboxylase is a homotetramer with four domains and about 1200 amino acids. A truncated construct of pyruvate carboxylase from *Rhizobium etli* has 632 amino acids and is primarily comprised of the carboxyltransferase domain. It has 32 helices and 16 beta sheets. Thr882 shuttles a proton between the biotin cofactor and pyruvate, while Arg 548, Gln552 and Arg621 stabilize the enolpyruvate intermediate. Asp590 and Tyr628 form a binding pocket where carboxybiotin cofactor is inserted into the active site. All of these amino acids may react with experimental inhibitors. The active site is centered on the ligand Zinc²⁺, and while pyruvate does not directly bind to Zn²⁺, the ion affects the orientation of the pyruvate in the binding site. The Saint Joan Antida High School SMART (Students Modeling A Research Topic) team designed a model of the carboxyltransferase domain of pyruvate carboxylase using 3D printing technology to study structure-function relationships and model novel inhibitors. Ongoing research should continue to seek inhibitors that will shut down pyruvate carboxylase, potentially leading to new cancer treatments.



Specific Model Information:

Amino acid side chains involved:

- Thr882 is colored orange. It moves a proton from pyruvate to enolate during the carboxylation process.
- Arg548, Gln552, Arg621 are colored paleturquoise. They stabilize the enolpyruvate intermediate.
- Asp590 and Tyr628 are colored pink. They form a binding pocket that allows for the insertion of carboxybiotin into the active site.

Highlighted protein structures:

- Alpha helix structures are colored tomato
- Beta sheet structures are colored mediumorchid
- Hydrogen bonds are colored lightyellow
- The allosteric domain is colored white
- Loops in carboxyltransferase domain are colored deepskyblue

Supporting Features:

- Struts are colored beige

CBM SMART Teams Website:

<http://cbm.msoe.edu/smartTeams/smartTeamsLocal.php>