

Groundbreaking study on complex movements of enzymes

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A groundbreaking study has revealed in great detail how enzymes in the cell cooperate to make fat. These enzymes are integrated into a single molecular complex known as fatty acid synthase. This complex is regarded as a potential target for developing new anti-obesity and anti-cancer drugs.

Dr. Stuart Smith, at Children's Hospital Oakland Research Institute, collaborated with Drs. Edward Brignole and Francisco Asturias from The Scripps Research Institute in La Jolla, Calif. in a study published in the February 2009 edition of *Nature Structural and Molecular Biology* and featured on the cover of the journal.

"Fatty Acid Synthase is a remarkably complex structure. It contains all of the components needed to convert carbohydrates into fat," Dr. Smith explained. "We have suspected for some time that the enzyme complex is extremely flexible, which makes it difficult to analyze using X-ray crystallography. Last year the X-ray structure of the complex was solved by a group in Switzerland, but this structure provided only a snapshot of the complex in one of its many poses. We were able to use state-of-theart electron microscopy to obtain images of the complex in many of its different conformations and assemble these images into a movie that displays the full range of motion of the components of the complex." The results reveal how enzymes that appear distantly located in the X-ray structure are able to make the contacts with each other needed for catalysis. The extraordinary swinging, swiveling and rolling motions of fatty acid synthase are represented on the cover of the journal in the



form of a flamenco dancer.

Some pharmaceutical companies are focusing on inhibitors of fatty acid synthase because they are known to block the conversion of carbohydrates into fat and suppress appetite as well as slow the growth of cancer cells. Structural information garnered from X-ray and electron microscope images may aid in the design of more effective inhibitors that could be used therapeutically.

Source: Children's Hospital & Research Center at Oakland

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