Translating form into function

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In the last 40 years, scientists have perfected ways to determine the knot-like structure of enzymes, but they've been stumped trying to translate the structure into an understanding of function – what the enzyme actually does in the body. This puzzle has hindered drug discovery, since many of the most successful drugs work by blocking enzyme action. Now, in an expedited article in *Nature*, researchers show that a solution to the puzzle is finally in sight.

A team co-led by UCSF's Brian Shoichet, Steven Almo of the Albert Einstein College of Medicine, and Frank Raushel of Texas A&M describes the first success "decrypting" an enzyme's function from its structure. If their new strategy works with other enzymes, it should become a potent tool to determine how key enzymes work in the body. And since enzyme action is crucial to disease, the technique opens an efficient route to drug discovery, Shoichet say.

Schoichet a professor of pharmaceutical chemistry and an investigator in the California Institute for Quantitative Biomedical Research, or QB3, based at UCSF.

The team's success came by modifying a technique called molecular docking, a computer-aided modeling strategy used to search for potential drugs. Docking works by allowing researchers to first determine the atom-by-atom structure of an enzyme and then screen many thousands of molecules for one that fits into the empty "active site" of the enzyme.

Shoichet calls this a search for the missing piece of a jigsaw puzzle. A

molecule that fits the enzyme's active site will block its activity – just what many promising drugs do.

The strategy works well for one kind of drug discovery -- finding molecules to fit in the active site and physically block enzyme action. But the research team sought to divine from an enzyme's structure just what natural molecule triggers the enzyme into action -- fitting into the active site and enabling the enzyme to act as a catalyst. This was a search for the so-called substrate for the enzyme, a search that has never succeeded simply from knowing an enzyme's configuration.

The key to the team's success was a computational feat: simulating candidate substrates that mimicked unstable "intermediate" molecules – those that exist only briefly as the catalyst turns the substrate into a new molecule.

Because these intermediates are unstable, scientists have until now been unable to test their fit to the enzyme's active site.

Once the scientists had predicted the substrate, Raushel, a professor of chemistry at Texas A&M University, tested the prediction experimentally. The results confirmed the prediction. Almo, a professor of biochemistry at Albert Einstein College of Medicine, further confirmed the finding by determining the substrate's atomic level structure through x-ray crystallography.

"To tell the truth, we were very surprised that the docking approach worked to determine the substrate," says Shoichet. "There's so many ways that the approach can go wrong. We're all very gratified."

For their experiments, the team extracted an enzyme from a bacterium known as Thermotoga maritima, a microbe that normally lives at very high temperatures and pressures near volcanic ocean vents. Its structure

was determined as a part of the structural genomics project, a large-scale, worldwide effort to determine the structures of enzymes and receptors.

With the nature of the substrate in hand, the scientists went on to discover that the enzyme works in a previously uncharacterized metabolic pathway in bacteria.

Source: University of California - San Francisco