

SOUTHWESTERN NEWS

Media contact: Susan A. Steeves

(214) 648-3404

susan.steeves@email.swmed.edu

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UT SOUTHWESTERN RESEARCHERS DEVELOP TECHNIQUE TO DETERMINE PROTEIN COMMUNICATION, FUNCTION

DALLAS – October 8, 1999 – UT Southwestern Medical Center at Dallas researchers report in today's *Science* on their new mathematical formula to map the transfer of energy, the communication method of molecules, from one area of a protein to another.

Because scientists expect to locate all genes in the human genome within the next two years, it's vitally important to have an efficient, fast way to understand protein function in order to design more effective drugs for a vast number of diseases, said Dr. Rama Ranganathan, assistant professor of pharmacology and a Howard Hughes Medical Institute investigator.

"We devised a statistical technique to tell how two positions in a protein interact with each other," Ranganathan said. "We wanted to find out how one position in a protein talked with another."

Ranganathan and his collaborator, pharmacology graduate student Steve Lockless, suspected that individual molecules contained communication pathways since information moves in through a series of protein-protein interactions in cellular-signaling pathways. They knew that when one protein activates another, the points at which they receive and send messages are sometimes distant in molecular terms. But it seemed unlikely to them that the protein underwent a complete restructuring to accomplish this information transfer.

Ranganathan compared communication between different molecular positions with an automobile.

"If I push the brake in my car to stop it, the whole front end could undergo a complete structural change and collapse, causing it to rub against the wheels until the vehicle stops. But that would be very inefficient and, in fact, is not how it works," he said. "We use hydraulics to make the car stop; the rigid tubes carry the flexible fluid. We push the brakes gently, and it's

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interpreted as a significant structural change at the brakes.

"In exactly the same way it makes sense that pathways that sense signals on the protein at one site then move the energy along to communicate it at another site a long distance away."

Using a protein molecule, the PDZ domain, that exists in most living organisms, Lockless and Ranganathan studied the distribution of amino acids at various sites in the molecule to determine which ones were communicating. Using that information, the investigators developed a mathematical formula to test how one position talks to every other position on the protein.

They tested their technique by comparing its results with those of a slow but proven method of determining protein function, mutagenesis. This supported the mathematical formula.

"Using our statistical method, we found these beautiful pathways, just like the conduits that we conjured originally, which are communicating right through the core of the protein and out the other side," Ranganathan said.

This will help researchers determine the functional parts of the protein although it still doesn't reveal the physical mechanism that triggers the energy connection.

Ranganathan cautioned, however, that the new statistical technique must be tested on many different proteins to determine whether it can be used practically to build synthetic proteins and manipulate proteins to build better drugs.

Partial support for this work came from the Burroughs-Wellcome Fund New Investigator Award in Basic Pharmacological Sciences.

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