Researchers design a better way to discover drug candidates

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(PhysOrg.com) -- Yale researchers have devised a novel way to trick cells into getting rid of problematic proteins, a method that could help pharmaceutical companies quickly identify promising targets for new drugs.

"Our new approach offers great potential in overcoming a key stumbling block in drug development today: the validation of drug target proteins in living organisms," said Craig Crews, the Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology, professor of chemistry and pharmacology, member of the Yale Cancer Center and senior author of the study.

The work is reported online July 3 in the journal *Nature* Chemical Biology.

Drug companies spend hundreds of millions of dollars to design small molecules that fit into folds of proteins and inhibit their function. The new technique developed by Crews and his team will help determine which of these proteins are good targets for drug development.

The research team decided to mimic the cell's natural quality control mechanisms that mark defective proteins for destruction. They created a chemical compound that resembles a partially denatured protein, a state that triggers cellular mechanisms to slice up a protein. The team then attached the compound, which Crews says resembles a "greasy knob," to proteins of interest. Using green fluorescent markers, the team found

that the technique destroyed a variety of protein types in both cell culture and in live animals.

Crews said the technique has many advantages over existing target validation strategies.

"This strategy also has general utility in controlling protein function and we believe it will undoubtedly have many new unforeseen applications," Crews said.

Provided by Yale University