Scientists find a way to make disease-causing proteins vulnerable to drugs

July 27 2012, By Bill Hathaway

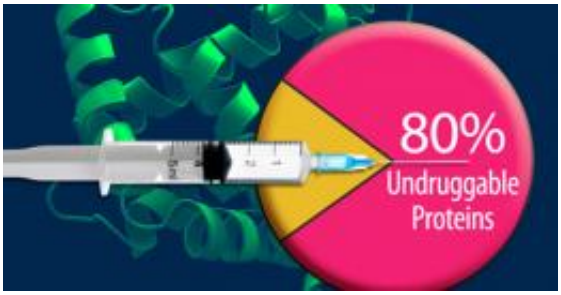

Illustration by Michael Helfenbein

(Phys.org) -- One of the most daunting challenges facing pharmaceutical scientists today are “undruggable proteins” – the approximately 80% of proteins involved in human disease that do not interact with current drugs.

Yale researchers have identified a novel way to design drugs for these previously inaccessible proteins. The research was published July 26 in the journal *Chemistry & Biology*.

“There is enormous interest in molecules that can both traverse cell membranes and inhibit interactions between proteins,” said Alanna Schepartz, the Milton Harris '29 Ph.D. Professor of Chemistry, director of the Yale Chemical Biology Institute and senior author of the paper. “Proteins and polypeptides are very good at inhibiting interactions

between proteins in a test tube. We have identified a signal that helps these proteins enter the cell."

Most drugs today are very small molecules and fit snuggly into relatively deep pockets in a protein, usually to inhibit a chemical reaction. But many proteins involved in disease do not perform chemical reactions. Instead they bind to other proteins, or DNA, or RNA. It has proven extremely difficult to design small molecules that inhibit these binding interactions.

Although proteins are used as drugs today, they operate almost exclusively in areas outside the cell, not within the cells where many disease processes originate.

Schepartz and her team identified a molecular signal that allows potentially therapeutic proteins to hitch a ride into cells using vesicles, or small packets of molecular information that fuse with membranes of cells in a process called endocytosis. The signal helps the protein escape from the vesicle to reach the interior of the cell.

"We are very interested to understand how this release signal works, as it may allow researchers to engineer molecules to follow a prescribed pathway into cell," Schepartz said.

Other Yale authors are Jacob S. Appelbaum, Jonathan R. LaRochelle, Betsy A. Smith, Daniel M. Balkin and Justin M. Holub.

The research was funded by the National Institutes of Health.

Provided by Yale University