By creating molecular 'bridge,' scientists change function of a protein

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By designing a molecular bridge, scientists at the University of Illinois at Urbana-Champaign have forged a successful pathway through a complex ocean of barriers: They've changed the function of a protein using a co-evolution approach.

In a study to be published in the Journal of Molecular Biology, doctoral student Zhilei Chen and Huimin Zhao, a professor of chemical and biomolecular engineering, describe what they call a "simple and efficient method for creation of novel protein functions in an existing protein scaffold."

In doing so, Zhao and Chen skirted the two time-and-labor-consuming approaches tried repeatedly in the past decade: rational design, which requires extensive knowledge of protein folding, structure, function and dynamics; and directed evolution that mimics natural evolution in a test tube but may require the screening of an astronomical number of mutants for the creation of new protein functions.

"We now provide one possible solution to a long-lasting barrier that is important in the protein engineering area – that is the creation of the new protein functions," Zhao said. "Our approach is to build a bridge between the existing protein function to the target new function by adding some intermediate functions followed by stepwise directed evolution of these intermediate functions. If done, it gives you the ability to create protein functions for any purpose you want – as a catalyst to create new chemicals that might be useful in such things as therapeutics,

for example.”

By way of in-vitro co-evolution, the researchers gradually changed the function of the human estrogen receptor alpha, a nuclear hormone receptor mostly expressed in the prostate, ovary and urinary tract. What they did was modify the estrogen receptor in a step-wise fashion, Zhao said. They used testosterone and progesterone to build the bridge.

The receptor was gradually altered to accept one steroid, then another, until accepting the desired one – corticosterone, a potent glucocoticoid. In total, Zhao and Chen did four rounds of random mutagenesis and screened about 1 million mutants before they found two estrogen receptor mutants that can be activated by corticosterone. The whole process was done in a couple of months.

The authors conclude that their new method may provide “a general approach to engineering biomolecules and biosystems such as receptors, enzymes, antibodies, ribosymes, DNAzymes and viruses with novel functions.”
Zhao is a member of the Institute for Genomic Biology and the Center for Biophysics and Computational Biology at Illinois. He also is an affiliate in the chemistry and bioengineering departments.

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Source: University of Illinois at Urbana-Champaign