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Enzymes from scratch

Reporting in *Science*, researchers at UC Santa Barbara, UCSF and the University of Pittsburgh have developed a new workflow for designing enzymes from scratch, paving the way toward more efficient, powerful and environmentally benign chemistry. The new method allows designers to combine a variety of desirable properties into new-to-nature catalysts for an array of applications, from drug development to materials design. This research is the result of a collaborative effort between the DeGrado lab at UCSF, the Yang lab at UCSB and the Liu lab at the University of Pittsburgh.

“If people could design very efficient enzymes from scratch, you could solve many important problems,” said UCSB chemistry professor Yang Yang, a senior author on the paper. De novo design of enzymes could, for instance, overcome limitations in function and stability found in natural catalysts without losing their inherent selectivity and efficiency.

“For fundamental research, chemists and biologists have long been hoping to have the ability to design enzymes from scratch.”

Bespoke protein catalysts

Catalysts, both biological and synthetic, are the workhorses of chemistry. They’re responsible for enabling and accelerating the reactions that change the structures of target molecules. Enzymes in particular are “nature’s privileged catalysts,” according to Yang, because of the level of selectivity and efficiency these proteins

have in catalyzing reactions.

However, natural enzymes tend to function under narrow conditions, favoring only certain molecules in certain environments. To bring the power of biocatalysis to more molecules, scientists are turning to de novo protein design, a bottom-up approach that uses amino acid building blocks to create proteins with specific structures and functions. The relatively small size of de novo proteins provides favorable efficiency relative to most enzymes; their excellent thermal and organic solvent stability can allow a wider range of temperatures and up to 60% of organic solvents, and it becomes possible to use a variety of cofactors, including those that are not found in nature, to further optimize the proteins for the desired result.

“So here, working with Bill DeGrado’s group at UCSF and Peng Liu’s group at Pitt, we have a workflow to convert a very simple and miniature helical bundle protein into very efficient and very selective enzymes to catalyze synthetically useful reactions,” Yang said of the researchers’ proof-of-concept. The project entailed using de novo protein design to create enzymes that can form carbon-carbon, or carbon-silicon bonds, for which “there is a lack of efficient natural enzymes,” according to Yang.

Using the helical bundle protein as a framework, they then used state-of-the art artificial intelligence methods to design sequences of amino acids that underlie the protein structures with the desired functionalities and properties to turn the bundle into an enzyme.

“The earlier variants were reasonable catalysts, but they were not the best because the efficiency and selectivity were modest,” Yang said of the initial results. Based on X-ray crystallography of the resulting protein, they found a “disorganized loop” in the structure where it was supposed to be a well-organized helix. A second round of design, using a loop searching algorithm this time, resulted in four of 10 designs with high activity and excellent stereoselectivity.

“In other words, although AI-based protein design methods are very useful, to have very good catalysts we still have to use our in-house algorithm and our chemical intuition to get everything done the right way,” Yang said.

The success of this project demonstrates that de novo protein design can be a powerful tool in catalysis, one that can give chemists more efficient and selective reactions as well as products that aren’t as easily reached with natural enzymes or

small-molecule synthetic catalysts.

“If you really understand the design principles, then you can build a protein catalyst to use whatever cofactors you would like to use, and to achieve challenging transformations in water, the greenest solvent, as the reaction medium,” Yang said.

Further work in the Yang lab, in collaboration with both the DeGrado lab and the Liu lab, will involve exploring ways to mimic natural enzyme function with simpler, smaller but equally active de novo enzymes, and to generate de novo enzymes that operate via mechanisms not previously known in nature.

Research in this paper was conducted by Kaipeng Hou, Wei Huang, Miao Qui, Thomas H. Tugwell, Turki Alturaifi, Yuda Chen, Xingjie Zhang, Lei Lu, and Samuel I. Mann.

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