Researchers reconstitute enzyme that synthesizes cholesterol drug lovastatin

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Researchers from the UCLA Henry Samueli School of Engineering and Applied Science have for the first time successfully reconstituted in the laboratory the enzyme responsible for producing the blockbuster cholesterol-lowering drug lovastatin.

The research, published Oct. 23 in the journal *Science*, could potentially lead to the development of other compounds with similarly beneficial effects.

The lovastatin-synthesizing enzyme is one of the most interesting but least understood of the polyketide synthases, which are found in filamentous fungi and which play a crucial role in the synthesis of "small molecule natural products" — pharmacologically or biologically potent compounds produced by living organisms, many of which are the active ingredients in pharmaceuticals.

Commonly used antibiotics, such as tetracycline, are produced by polyketide synthases. Polyketides represent a class of 7,000 known structures, of which more than 20 are commercial drugs, including the immunosuppressant rapamycin, the antibiotic erythromycin and the anticancer drug doxorubicin.

"In this study, we studied the enzyme that makes a small-molecule precursor to lovastatin. And what's really different about this enzyme, compared to all other enzymes people have studied, is that this enzyme is extraordinarily large," said Yi Tang, associate professor of chemical and

biomolecular engineering. "It's one of the largest enzymes ever to be reconstituted in a test tube. It is 10 times the size of most enzymes people study."

The enzyme used in Tang's study has seven active sites and catalyzes more than 40 different reactions that eventually result in an important precursor to lovastatin.

By understanding how this large assembly line works, Tang's team hopes to retune the assembly line to be able to produce other natural products — something nature doesn't currently do.

"It's like having an assembly line with seven stations, and in one round you have to go through a combination of these seven stations. Remarkably, this enzyme uses the assembly line eight times to make this small molecule — every time, it uses a different combination of the individual stations," Tang said. "So the large enzyme is programmed to utilize these stations differentially at every cycle, in different combinations, and now we can do it in a test tube."

Tang's team has been able to recapture all of the steps needed to make the lovastatin precursor molecule. And with this, Tang hopes they will be able to disrupt, tweak and change some of the steps to make slightly different molecules that can be just as beneficial.

"It's biosynthetic engineering of an assembly line to make a molecule that nature doesn't make," Tang said. "So our eventual goal, once we understand how the enzyme works, is to rationally manipulate the individual stations or manipulate how a set of stations is used in each iteration to generate new compounds that nature doesn't make that will result in new activities, new molecules."

Source: University of California - Los Angeles