MedicalXpress

Single-step fermentative method for the production of cholesterol-lowering drug pravastatin

February 27 2015

In a study published in *Proceedings of the National Academy of Sciences*, the researchers have devised a single-step fermentative method for the industrial production of the active drug pravastatin that previously involved a costly dual-step fermentation and biotransformation process.

Reprogramming the antibiotics-producing fungus Penicillium chrysogenum, with discovery and engineering of a cytochrome P450 enzyme involved in the hydroxylation of the precursor compactin, enabled high level fermentation of the correct form of pravastatin to facilitate efficient industrial-scale statin drug production.

Key steps leading to the successful outcome included the identification and deletion of a fungal gene responsible for degradation of compactin, in addition to evolution of the P450 to enable it to catalyse the desired stereoselective hydroxylation step required for high level pravastatin production.

Statins are successful, widely used drugs that decrease the risk of coronary heart disease and strokes by lowering cholesterol levels. The development of this group of drugs has been one of the major breakthroughs in human healthcare over the last two decades.

Statins have their origins in the discovery of a fungal natural product (compactin), which was shown to have good cholesterol lowering

properties. Since compactin itself was not stable enough for clinical use, derivatives were created and other molecules with a similar mode of action were prepared to provide useful drugs.

Professor Andrew Munro based at the Manchester Institute of Biotechnology at The University of Manchester said: "This research marks a significant breakthrough and forms the basis of a patented process for the efficient production of this blockbuster drug. These results are the first example of harnessing the potential of a previously improved industrial production strain which can be used in the rapid development of other novel production strains for unrelated chemicals.

"The data also highlight how protein engineering can be exploited in synthetic biology applications towards industrial scale production of valuable pharmaceuticals."

More information: "Single-step fermentative production of the cholesterol-lowering drug pravastatin via reprogramming of Penicillium chrysogenum." *PNAS* 2015 ; published ahead of print February 17, 2015, DOI: 10.1073/pnas.1419028112

Provided by University of Manchester