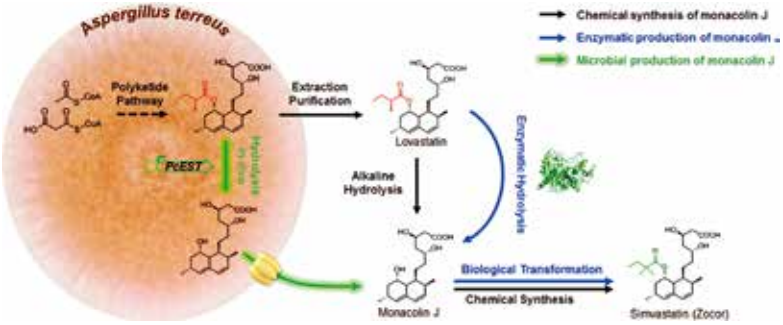
One Step Closer Towards Complete Bioproduction of Zocor

Simvastatin (Zocor) is one of the most pharmaceutically important cholesterol-lowering drugs with annual sales exceeding $3 billion in 2015. The industrial production of simvastatin usually includes three steps: microbial production of lovastatin through *Aspergillus terreus* fermentation, alkaline hydrolysis of lovastatin to produce monacolin J, and chemical transformation of monacolin J to simvastatin. A whole-cell biocatalysis process was developed for the conversion process of monacolin J to simvastatin, which won the Presidential Green Chemistry Challenge Awards in 2012.

However, alkaline hydrolysis is still used to convert lovastatin to monacolin J in the simvastatin industrial process, which is complex, laborious, and polluting. Therefore, an environment friendly manufacturing technique is more promising. In fact, several research groups including one at Merck have attempted to develop alternative processes for the production of monacolin J from lovastatin through both in vitro enzymatic hydrolysis and in vivo microbial transformation. Unfortunately, none of these process improvements were applied at an industrial-scale due to very low efficiency.

Recently, researchers at the Qingdao Institute of Bioenergy and Bioprocess Technology, Chinese Academy of Sciences have worked with coworkers from Hisun Pharm, the world's largest lovastatin/simvastatin producer, to develop a single-step microbial production process for monacolin J by the engineering of an industrial lovastatin-producing *A. terreus* strain. This technical route is more simple and environment friendly, which makes complete bio-production of simvastatin feasible and promising. Obviously, it is an important and valuable process improvement, which will be beneficial for the current simvastatin industry and hypercholesterolemia market.

In their study, a new lovastatin hydrolase PcEST which cloud cleave the side chain of lovastatin to produce monacolin J was identified from *Penicillium chrysogenum*. Compared with the previously patented one, PcEST possesses a nearly 232-fold higher catalytic efficiency, and the amino acid sequence identity is just 16.8%. These results demonstrated that PcEST is an efficient lovastatin hydrolase with independent intellectual property rights, which are important for its applications. To test the feasibility and efficiency of direct in vivo microbial production of monacolin J, the above PcEST enzyme was heterologously expressed in the industrial lovastatin-producing *A. terreus* strain using the strong promoter PgpdAT. Excitingly, approximately 95% of the biosynthesized lovastatin was successfully hydrolyzed to monacolin J in vivo. This genetic engineering mutant will be an efficient and practical microbial cell factory to directly produce monacolin J through single-step fermentation, and would be easily applied to industrial production with the existing equipment and fermentation process of lovastatin production.



An overview of the production process of simvastatin.

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