

Tools for engineering complex natural product pathways in bacteria

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Secondary metabolites, which are products of complex chemistries found in nature, represent a vast number of chemical candidates (>200,000) for a myriad of applications such as drugs, food additives, consumer products, industrial chemicals, and biofuels. Most biologically-active natural products are chemically complex and heavily functionalized molecules with multiple chiral centers. The structural complexity of natural products precludes the development of economical synthetic routes to these molecules, and procuring marketable quantities of these substances from their natural sources is equally challenging. Therefore, developing microbial biocatalysts for the production of secondary metabolite natural products is one of the high priority agenda for metabolic engineering and synthetic biology research.

Recent progress in synthetic biology and metabolic engineering offers new opportunities for engineering complex biosynthetic pathways in microbial hosts. We developed a new metabolic engineering approach, multivariate modular metabolic engineering (MMME), for systematically engineering such complex pathways. Recently, we expanded the scope of our approach to quick construction and optimization of orthologous pathways for the selection of best variant biosynthetic routes from nature. Here, we focus on the development of MMME tools and its application to biosynthesis of complex natural products, specifically terpenoids in bacteria.