ENGINEERED ENZYMES, PATHWAYS, AND TOOLS FOR THE BIOSYNTHESIS OF NON-NATURAL POLYKETIDES AND TERPENES

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Many clinically used drugs are derived from secondary metabolites that are biosynthesized in a modular fashion by the selection and assembly of small molecule building blocks. Chimeric biosynthetic pathways can be constructed in an attempt to produce analogues for drug discovery. Yet, the scope and utility of this combinatorial approach is limited by the inherent substrate specificity and poor functional modularity of most biosynthetic machinery. Here, our approach to expanding the scope of polyketide and isoprenoid combinatorial biosynthesis by leveraging enzyme engineering and synthetic biology will be summarized. Our recent advances that realize the installation of multiple extender units into polyketides by engineered polyketide synthases will be presented, in addition to genetically encoded biosensors that enable directed evolution of natural product biosynthetic machinery in living cells. Furthermore, an artificial biosynthetic pathway for the biosynthesis of isoprenoids is described that utilizes non-natural building blocks and can support high titers of non-natural isoprenoids in *E. coli*. Our synthetic biology approach expands the synthetic capabilities of natural product diversification strategies and provides an improved understanding of the molecular basis for specificity in complex molecular assemblies.