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Production of novel synthetic natural products by engineering of fungal PKS-NRPS hybrids

Filamentous fungi are prolific producers of a large number of bioactive and structurally diverse secondary metabolites. These include compounds of mixed biosynthetic origin such as cytochalasin E, where the PKS-NRPS encoding gene ccsA from *Aspergillus clavatus* has been shown to be involved in the biosynthesis of the core backbone of the molecule [1]. Here, we will present our efforts towards biocombinatorial synthesis of novel natural products through engineering of the cytochalasin E pathway. First, co-expression of CcsA with a trans-acting enoyl reductase CcsC encoded in the same *A. clavatus* gene cluster resulted in a Diels Alder derived product when expressed in *A. nidulans*. Secondly, we have identified a compound structurally similar to the CcsA/CcsC product by co-expression of the PKS-NRPS Syn2 with the enoyl reductase Rap2 from *Magnaporthe oryzae*. With the goal of synthesizing novel synthetic natural products, we constructed a CcsA-Syn2 chimeric enzyme and successfully produced the expected new product of mixed polyketide-nonribosomal origin. Thus, swapping of the entire CcsA NRPS module with the corresponding NRPS module from Syn2, led to the production of a compound with the CcsA-specific polyketide backbone attached to the tryptophan residue provided by the Syn2 NRPS. The reciprocal cross (Syn2 PKS and CcsA NRPS) also led to production the expected chimeric product. Furthermore, we have demonstrated that the length and amino acid sequence of the inter-modular linker is not crucial for preserving PKS-NRPS function.

[1] Qiao, K.; Chooi, Y.-H.; Tang, Y.I. (2011). Metabolic Engineering, 13, 723-732.