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Published in:

Book of abstracts from the 13th European Conference on Fungal Genetics

Publication date:

2016

Document Version

Publisher's PDF, also known as Version of record

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Citation (APA):

Nielsen, M. L., Petersen, T. I., Mortensen, U. H., Andersen, M. R., Hoof, J. B., & Larsen, T. O. (2016). Production of novel synthetic natural products by engineering of fungal PKS-NRPS hybrids. In Book of abstracts from the 13th European Conference on Fungal Genetics (pp. 453-453). [CS5T68]

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POSTER SESSION ABSTRACTS
Session CS5 Applied genomics and biotechnology
CS5T68

Tuesday 5th April
14:00 - 16:00

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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.