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In vivo engineering of polyketide synthases

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Introduction
Polyketides form the basic building blocks of numerous natural products, which are in use in pharmaceuticals, food additives and other fine chemicals. Polyketides derived from fungi are formed by type I iterative PKSes (iPKSes). The common domain structure of a non-reducing PKS (NR-PKS) is SAT-KS-AT-PT-ACP-TE, which enables the NR-PKS to produce very complex polyaromatic compounds. Studies have revealed the general catalytic properties of these domains, and for some even the specificity can be predicted based solely by bioinformatics.1,2

Some attempts have been made to investigate and engineer NR-iPKSes, but these have focused on in vitro assays.1,2 To speed up construction and screening the present study focuses on in vivo analysis in S. cerevisiae of native and engineered iPKSes. To engineer the NR-iPKSes the combination of SAT-KS-AT and PT-ACP-TE tridomain units of different origin should create new compounds. The used linker between the tridomain units has been designed by multiple alignment of all the studied NR-iPKSes and by HMM investigation of the region between the AT and PT domains. This revealed a 12 amino acid long conserved region. This region is used as a uniform linker in the synthetic chimeric iPKSes as it will not extend the overall amino acid chain, thus native protein structure should be conserved.

Overview of investigated iPKSes
The domain structure, product length and first ring formation are shown. Right column requires an unloading enzyme as the iPKSes are lacking a TE/RED domain.

Chemical logic of chimeric iPKSes
The SAT-KS-AT tridomain is proposed to control chain length while PT-ACP-TE domain control the folding pattern. By combining non-native tridomains it may be possible to engineer novel polyketide scaffolds.

References