Rational design of modular polyketide synthases: morphing the aureothin pathway into a luteoreticulin assembly line.

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Abstract

The unusual nitro-substituted polyketides aureothin, neoaureothin (spectinabilin), and luteoreticulin, which are produced by diverse Streptomyces species, point to a joint evolution. Through rational genetic recombination and domain exchanges we have successfully reprogrammed the modular (type I) aur polyketide synthase (PKS) into a synthase that generates luteoreticulin. This is the first rational transformation of a modular PKS to produce a complex polyketide that was initially isolated from a different bacterium. A unique aspect of this synthetic biology approach is that we exclusively used genes from a single biosynthesis gene cluster to design the artificial pathway, an avenue that likely emulates natural evolutionary processes. Furthermore, an unexpected, context-dependent switch in the regiospecificity of a pyrone methyl transferase was observed. We also describe an unprecedented scenario where an AT domain iteratively loads an extender unit onto the cognate ACP and the downstream ACP. This aberrant function is a novel case of non-colinear behavior of PKS domains.

Beteiligte Forschungseinheiten

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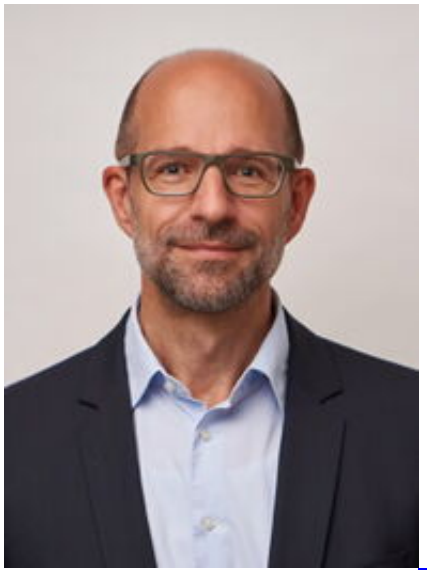

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