ACS SyntheticBiology

In This Issue

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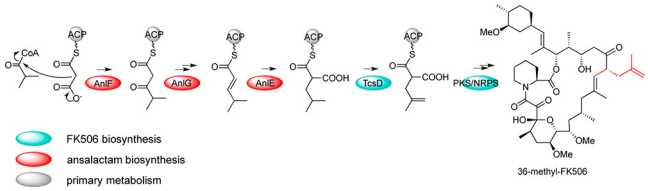
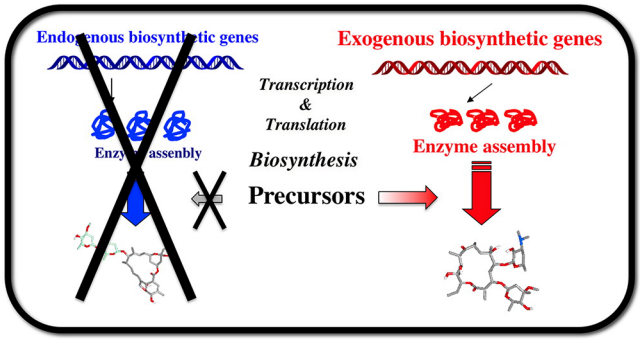
POLYKETIDE PRECURSOR PATHWAY ENGINEERING



FK506 is a clinically relevant drug that acts as an immunosuppressant. The bacterial natural product is assembled by the polyketide synthase (PKS) FkbA-C and nonribosomal peptide synthetase FkbP enzyme complex. While polyketide backbones have been engineered successfully in the past, most efforts have focused on the structurally related immunosuppressants, FK520 and rapamycin. Now, Lechner et al. (DOI: 10.1021/sb3001062) describe the successful biosynthesis of an engineered FK506.

Here, the authors used a co-opted gene cassette encoding isobutyrylmalonyl-CoA biosynthesis to strategically introduce a methyl group in the macrolide structure, resulting in an FK506 with improved biological activity.

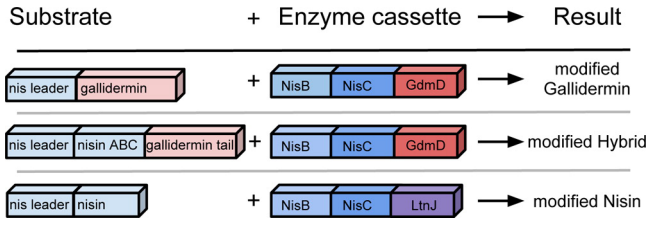
ENGINEERED *STREPTOMYCES* FOR SECONDARY METABOLITE BIOSYNTHESIS



Streptomyces are a rich source of pharmaceutical compounds; defined biochemical pathways enable these bacteria to convert common cellular intermediates, such as sugars and fatty acids, into secondary metabolites including antibiotics. The identification and characterization of secondary metabolic gene clusters is essential for the elucidation of the mechanism of secondary metabolite biosynthesis. Here, Komatsu et al. (DOI: 10.1021/sb3001003) describe the construction of a model host for heterologous expression of biosynthetic gene clusters using engineered *Streptomyces avermitilis*.

The authors demonstrate the feasibility of using genetically engineered *S. avermitilis* as a heterologous host by the effective expression and production of 20 biosynthetic gene clusters for exogenous secondary metabolites.

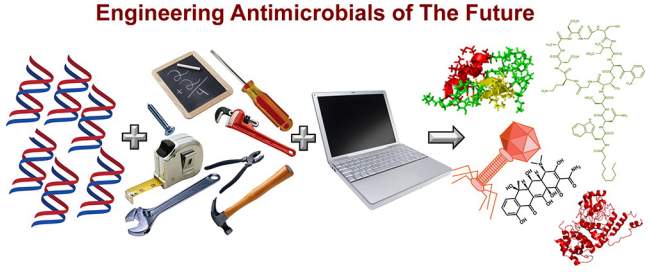
DESIGNING NEW-TO-NATURE ANTIMICROBIAL PEPTIDES



Lantipeptides are peptides with several post-translationally modified amino acid residues that commonly show antimicrobial activity. In this study, van Heel et al. (DOI: 10.1021/sb3001084) modify these lantibiotics, using a synthetic biology approach to make hypermodified peptides containing over 20 canonical amino acids.

The authors combined different lantibiotic post-translational modification modules to act on a single substrate and demonstrate that additional modification enzymes (LtnJ a hydrogenase or GdmD a decarboxylase) can work together in an *in vivo* production system. This results in a plug-and-play system that can be used to select different sets of modification enzymes to work on diverse, specifically designed substrates.

SYNTHETIC BIOLOGY OF ANTIMICROBIAL DISCOVERY



The discovery of antibiotics represents one of the most important contributions to medicine, with most classes of antibiotics having been discovered during the midtwentieth century as natural products produced by soil-dwelling microbes. In this review, Zakeri and Lu (DOI: 10.1021/sb300101g) provide an overview of synthetic biological approaches to antimicrobial discovery.

Topics reviewed include small-molecule antibiotic discovery with considerations of genetic and protein engineering of natural product biosynthetic pathways, engineering of peptide antibiotics including nonribosomal peptides and antimicrobial peptides, and nontraditional therapeutics with discussions on engineering of phage and phage proteins for antimicrobial applications.

Special Issue: Natural Products: Tools and More

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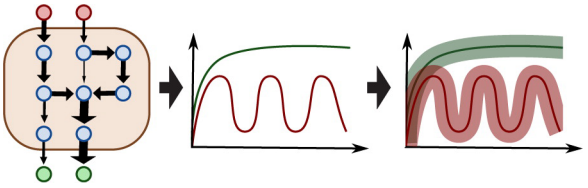
MODELING SECONDARY METABOLITE PRODUCTION



The successful engineering of secondary metabolite production relies on the availability of detailed computational models of metabolism. In this review, Breitling et al. (DOI: 10.1021/sb4000228) give us an overview of some of the specific computational modeling challenges faced in the engineering of secondary metabolism for enhanced natural product production.

The authors also emphasize the need for new concepts in quantitative modeling that can handle the lack of kinetic data and enzymatic characterization that is generally seen in natural products biosynthesis pathways.

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