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Editorial

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Natural Products: Tools and More Special Issue

The importance of discovering novel bioactive natural products has been emphasized repeatedly, in particular in the context of developing novel antimicrobial drugs. However, progress in this area has been slow. Synthetic biology is positioned to change this: the biosynthesis of most natural products is highly modular by evolutionary design, and biosynthetic mechanisms and chemical properties (activity, stability) have been polished to near perfection under strong selective pressure in a continuous chemical arms race in nature. We also now know that every newly synthesized genome reveals dozens of biosynthesis gene clusters that are "asleep" or cryptic, providing the building blocks for ambitious awakening-by-engineering approaches to access chemical novelty on a large scale. Synthetic biology not only allows the rapid exploitation of the natural diversity of bioactive molecules but also offers new routes to the creation of "unnatural" novel compounds. It has been argued that overall, the engineering of natural product biosynthesis is the area of synthetic biology closest to delivering successful commercial applications. This special issue features reviews on the recent advances in the synthetic biology of natural products and on metabolic modeling strategies to guide the engineering, two recent examples of the use of synthetic biology approaches for the diversification of natural products, as well as a paper on host and pathway engineering.

Zakeri and Lu provide a comprehensive overview of synthetic biology as applied to antimicrobial discovery, covering a very broad range of approaches, including the genetic engineering necessary for small-molecule development, such as the diversification of the functional groups that are responsible for the key biological activities, the engineering of antimicrobial libraries by use of computational approaches, and nontraditional therapeutics derived from engineered phage that target, for example, biofilms.

Van Heel et al. generated novel lantibiotics in *Lactoccocus lactis*. In addition to the natural lantibiotic biosynthesis system of this system, responsible for nisin production, they introduced either GdmD (a decarboxylase from *Staphyloccocus gallinarum* involved in gallidermin production) or LtnJ (a reductase that converts dehydroalanine into D-alanine and is involved in the production of lacticin 3147). In both cases, they succeeded in producing a novel lantibiotic with antibacterial activity. This indicates the strong possibility of producing lantibiotics with increased diversity and bioactivity by combining different post-translational modification modules from alternative lantibiotic production pathways and will be an important addition to the library of pathway parts.

Lechner et al. modify a natural product biosynthesis pathway to produce an unnatural variant of FK506, a commercially important immunosuppressant, using a newly identified three-gene cluster encoding for isobutyrylmalonyl-CoA biosynthesis from the genome sequence of *Streptomyces* sp. CNH189. These thee genes are naturally involved in the biosynthesis of ansalactam, which uses the unusual isobutyrate as a starter unit. They were introduced into a ketosynthase mutant of an FK506 producer, which had been used previously to produce the unnatural variant 36-methyl-FK506 by mutasynthesis, feeding 4-methylpentanoate to the cell. The heterologous expression of the new pathway resulted in the production of a 36-methyl-FK506, resulting from the use of the branched extender unit as an alternative to the natural substrate. Further exploitation of enzymes which use unusual starter units for polyketide synthesis will be of great interest for synthetic biology, as it will allow the expansion of the library of pathway parts for production of novel and diverse bioactive molecules.

Komatsu et al. introduced 5 different classes of biosynthetic pathways into an engineered strain of *Streptomyces avermitilis*, which had been optimized for natural product production by deleting large parts of the genome along with the endogenous biosynthesis gene clusters for avermectin, oligomycin, and filipin, the major metabolites produced by the *S. avermitilis* wild-type strain. Biosynthetic gene cluster for 8 polyketide pathways, 4 amino acid pathways, 4 sugar pathways, 3 shikimate pathways, and 5 MVA or MEP pathways were introduced into the engineered strain. In most cases the corresponding natural product was produced when the complete cluster was introduced, with only two cases requiring optimization of the gene expression by use of alternative promoters. Plant-derived genes, namely, the sesquiterpene synthase from *Artemisia annua* and diterpene synthases from *Taxus brevifolia* and *Ginkgo biloba*, were equally successfully expressed and produced the terpenes in the engineered host but required further engineering: codon optimization, using a constitutive promoter, and provision of the appropriate metabolic precursor. Of the biosynthesis gene clusters that were introduced into the engineered *S. avermitilis*, 7 compounds were chosen for further detailed study. In the case of pholipomycin (aminoglycoside), bafilomycin B1 (polyketide), lactacystin, holomycin (both use an amino acid pathway for precusors), and chloramphenicol (uses shikimate pathway for a precursor), the production in the wild-type *S. avermitilis* was greater than the original producer strain by up to 12-fold, and compared to the wild-type *S. avermitilis*, the production was higher by up to 2.5-fold. These results suggest the great opportunity for *Streptomyces* to be engineered as a chassis for the effective screening and production of bioactive molecules derived and combined from various natural sources.

Our own team describes new computational modeling strategies for the synthetic biology of secondary metabolite production, emphasizing 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. Modeling methods that can gracefully handle this uncertainty will be able to provide robust predictions that are essential for driving the rational engineering of high-producer strains for the large diversity of compounds

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illustrated in the papers by van Heel et al. and Lechner et al., taking universal host strains like the one presented by Komatsu et al. as a starting point.

Synthetic biology approaches to natural products biosynthesis are in their infancy, but as can be seen from the content of this special issue, there is progress in several key areas, from modeling and chassis engineering to expanding the chemical diversity by increasing the available libraries of pathway parts. We will surely see rapid advance within the next decade, with synthetic biology driving the next industrial revolution in biotechnology and making major steps toward its routine use as a tool for the green chemistry of natural product creation.

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Notes

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