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Author
Keasling, J

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Engineered Polyketide Synthases for Production of Commodity and Specialty Chemicals

Jay Keasling

Departments of Chemical Engineering and Bioengineering, University of California, Berkeley, CA 94720

Synthetic Biology Department, Physical Biosciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Joint BioEnergy Institute, Emeryville, CA 94608

Engineered modular polyketide synthases (PKSs) have the potential to be an extraordinarily effective retrosynthesis platform. Native PKSs assemble and tailor simple, readily available cellular acyl-CoAs into large, complex, chiral molecules. By successfully rearranging existing polyketide modules and domains, one could exquisitely control chemical structure from DNA sequence alone. As an example of the diverse biosynthetic potential of PKSs, we have concluded that approximately 20 of the roughly 150 commodity chemicals tracked by the petrochemical market information provider ICIS could be produced by mixing and matching naturally occurring PKS domains. To form these chemicals, engineered PKSs would load acyl- CoAs, perform a programmed number of extension reactions, and then release products using previously published mechanisms. However, this potential has only just begun to be realized as the compounds that have been made using engineered PKSs represent a small fraction of the potentially accessible chemical space. We envision a future in which a single design algorithm, using a molecule of interest as input, successfully combines natural PKS sequences to produce the desired molecule. This kind of algorithm could also be used to make analogs of existing natural products. In my talk, I will highlight work from our laboratory where we have engineered polyketide synthases to produce a variety of commodity and specialty chemicals.