

(SD2018-178) Engineering Polyketide Synthase Machinery in Synechococcus Cyanobacteria

Tech ID: 29938 / UC Case 2018-178-0

BACKGROUND

Complex polyketides include a family of natural products that possess a wide variety of pharmacological or biological activities. Numerous polyketides and their semisynthetic derivatives have been approved for clinical use in humans or animals, including antibiotics, antifungal agents, immunosuppressants, antiparasitic agents and insecticides. All these natural products share a common mechanism of biosynthesis and are produced by a class of enzymes called polyketide synthases (PKSs). Besides their essential role in the biosynthesis of a vast diversity of natural products, the versatility of PKSs can be further emphasized as they can be redesigned and repurposed to produce novel molecules that could be used as fuels, industrial chemicals, and monomers. Most polyketide producers are slow-growing, recalcitrant to genetic manipulation, or even non-culturable.

Cyanobacteria are particularly attractive for the production of natural compounds because they have minimal

nutritional demands and several strains have well established genetic tools.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego and Rosario National University (Argentina) have invented a novel functional heterologous PKS system expressed in a photosynthetic microorganism (cyanobacterium: *Synechococcus*). This patented technology, allows for the production of precursors and the expression of accessory proteins, and serves as a platform for production of a wide variety of polyketide products. These includes small molecules useful as medicinal natural products, biofuels, and polymer precursors.

The development of a photosynthetic PKS producing host will prove valuable for low cost, high volume

production of valuable small molecules, and we are currently evaluating culture scale-up on the +100 liter

level as proof of concept.

On the basis of this platform technology, other methylmalonyl-CoA derived polyketides could be produced in a sustainable and profitable manner by changing the third module with the desired PKS. Further, other PKS classes that require malonyl-CoA, ethylmalonyl-CoA, and other CoA precursors should be accessible by this approach. For additional details, please refer to the cited publication.

APPLICATIONS

This work is a foundational step forward for the production of high value polyketides in a photosynthetic microorganism.

ADVANTAGES

This invention is the first time that a functional heterologous PKS system has been expressed in a photosynthetic microorganism, *S. elongatus*

It is noteworthy that *S. elongatus* does not have its own PKS genes, thus acting as a biosynthetically naïve

host which offers superior genetic manipulation capabilities making it a clean host for polyketide production.

The development of a photosynthetic PKS producing host will prove valuable for low cost, high volume

production of valuable small molecules.

STATE OF DEVELOPMENT

The inventors are currently evaluating culture scale-up on the +100 liter level as proof of concept.

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OTHER INFORMATION

KEYWORDS

heterologous production,

Cyanobacteria, polyketide, PKS-

derived compounds, synthetic biology,

photosynthetic organism, Metabolic

Engineering, Genetically-Modified,

Synechococcus

CATEGORIZED AS

► [Agriculture & Animal Science](#)

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RELATED CASES

2018-178-0

UC San Diego is offering US patent rights for commercialization. It is available for licensing.

(12)	United States Patent Burkart et al.	(10) Patent No.: US 11,274,324 B2 (45) Date of Patent: Mar. 15, 2022
(54)	ENGINEERING POLYKETIDE SYNTHASE IN CYANOBACTERIA	
(71)	Applicant: The Regents of the University of California , Oakland, CA (US)	
(72)	Inventors: Michael D. Burkart , San Diego, CA (US); Jeffrey Mindrebo , San Diego, CA (US); James Golden , San Diego, CA (US); Arnaud Taton , San Diego, CA (US); Julia Roulet , Rosario (AR); Hugo Gramajo , Rosario (AR); Ana Arabolaza , Rosario (AR)	Begemann, M.B. et al. (Oct. 1, 2013). "An organic acid based counter selection system for cyanobacteria," <i>PLoS One</i> 8(10):e76594. Chen, Y. et al. (Dec. 2016, e-published Oct. 14, 2016). "Self-replicating shuttle vectors based on pANS, a small endogenous plasmid of the unicellular cyanobacterium <i>Synechococcus elongatus</i> PCC 7942," <i>Microbiology</i> 162(12):2029-2041. Dubendorf, J.W. et al. (May 5, 1991). "Controlling basal expression in an inducible T7 expression system by blocking the target T7 promoter with lac repressor," <i>J Mol Biol</i> 219(1):45-59. Ducat, D.C. et al. (Feb. 2011, e-published Jan. 5, 2011). "Engineering cyanobacteria to generate high-value products," <i>Trends Biotechnol</i> 29(2):95-103. Hughes, A.J. et al. (Feb. 25, 2011). "Enzymatic extender unit generation for in vitro polyketide synthase reactions: structural and functional showcasing of <i>Streptomyces coelicolor</i> MatB," <i>Chem Biol</i> 18(2):165-176. Ishikawa, F. et al. (Jan. 2012, e-published Dec. 29, 2011). "Dehydratase-specific probes for fatty acid and polyketide synthases," <i>J Am Chem Soc</i> 134(2):769-772. Khosla, C. et al. (1999). "Tolerance and specificity of polyketide synthases," <i>Annu Rev Biochem</i> 68:219-253. Ma, A.T. et al. (Nov. 2014, e-published Aug. 22, 2014). "Regulation of gene expression in diverse cyanobacterial species by using theophylline-responsive riboswitches," <i>Appl Environ Microbiol</i> 80(21):6704-6713. Mathur, M. et al. (Sep. 25, 1992). "Molecular cloning and sequencing of the gene for mycocerosic acid synthase, a novel fatty acid elongating multifunctional enzyme, from <i>Mycobacterium tuberculosis</i> var. <i>bovis</i> Bacillus Calmette-Guerin," <i>The Journal of Biological Chemistry</i> 267(27):19388-19395. Menendez-Bravo, S. et al. (Jul. 2014, e-published May 14, 2014). "Expanding the chemical diversity of natural esters by engineering a polyketide-derived pathway into <i>Escherichia coli</i> ," <i>Metab Eng</i> 24: 97-106. Murli, S. et al. (Aug. 2003, e-published Jul. 26, 2003). "Metabolic engineering of <i>Escherichia coli</i> for improved 6-deoxyerythronolide B production," <i>J Ind Microbiol Biotechnol</i> 30(8):500-509. Oliver, J.W.K. et al. (Jan. 22, 2013, e-published Jan. 7, 2013). "Cyanobacterial conversion of carbon dioxide to 2,3-butanediol," <i>PNAS USA</i> 110(4):1249-1254. Onwueme, K.C. et al. (Mar. 30, 2004, e-published Mar. 18, 2004). "Mycobacterial polyketide-associated proteins are acyltransferases: proof of principle with <i>Mycobacterium tuberculosis</i> PapA5," <i>PNAS USA</i> 101 (13):4608-4613.
(73)	Assignee: The Regents of the University of California , Oakland, CA (US)	
(*)	Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	
(21)	Appl. No.: 16/833,249	
(22)	Filed: Mar. 27, 2020	
(65)	Prior Publication Data US 2020/0332324 A1 Oct. 22, 2020	
	Related U.S. Application Data	
(60)	Provisional application No. 62/824,534, filed on Mar. 27, 2019.	
(51)	Int. Cl. C12P 17/16 (2006.01) C12N 9/00 (2006.01) C12N 9/90 (2006.01)	
(52)	U.S. Cl. CPC C12P 17/16 (2013.01); C12N 9/90 (2013.01); C12N 9/93 (2013.01); C12Y	

RELATED MATERIALS

- Roulet J, Taton A, Golden JW, Arabolaza A, Burkart MD, Gramajo H. Development of a cyanobacterial heterologous polyketide production platform. *Metab Eng*. 2018 Sep;49:94-104. doi: 10.1016/j.ymben.2018.07.013. Epub 2018 Jul 21. - 07/21/2018

PATENT STATUS

Patent Pending

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