Natural products research in the modern age

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Published in:
Synthetic and Systems Biotechnology

Link to article, DOI:
10.1016/j.synbio.2020.09.001

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Synthetic and Systems Biotechnology 5 (2020) 314–315

Contents lists available at ScienceDirect

Synthetic and Systems Biotechnology

journal homepage: http://www.keaipublishing.com/synbio

Editorial

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The sudden outbreak of COVID-19 clearly illustrates a complicated public health issue of global medicine shortages. We should not forget that besides the shortage of antivirals and vaccines there also is a lack of incentives for developing many other drugs, for example, antibiotics. Natural products produced by bacteria, fungi, and plants are one of the most important resources used by us for millennia. They have been developed as medicines, food additives, industrial materials, and so on. It is noteworthy that more than half of our antibiotics and anti-tumor drugs currently used in clinics are from natural products of *Actinomyces,* a group of gram-positive bacteria. Sadly, after the golden age of natural products research in the 1950s–1960s, the speed and outputs of natural products research have been dramatically slowing down. With advances in all aspects of biotechnology, we now are able to access natural products that were considered to be inaccessible. A gold mine is hidden in the genetic information of both culturable and unculturable microorganisms, waiting for us to exploit it.

The idea of organizing this Special Issue on Natural Products was inspired by the Novo Nordisk Foundation initiative Copenhagen Bioscience Cluster conference: Natural Products - Discovery, Biosynthesis, and Application, which was held in May 2019. A number of cutting edge research on natural products were presented in the conference. We strongly feel that it is about the right time to re-attract researchers' attention and reallocate resources to natural products discovery for valuable and bioactive compounds.

This special issue tries to cover a broad range (from computational biology to wet lab research; from bacterium, to yeast, to plant) of natural products, it comprises one perspective, six review articles and six original research papers that provide convincing signs that a new dawn of natural products research is coming.

In the perspective article, Prof. Deng and Dr. Tong reflect on the past and discuss potential courses for the future of natural products discovery. They are optimistic that another golden age of natural product-based drug discovery is coming [1].

In a classic "top-down" natural products research article, Devi and colleagues isolated *Bacillus velezensis* DTU001 from the indoor environment of the Technical University of Denmark, sequenced its genome, and found that it can produce iturin, fengycin and surfactin against the fungal pathogen *Candida albicans* [2].

The review by Zhong and colleagues focuses on the genome-mining based "bottom-up" strategy of natural products discovery. They systematically summarized bioinformatic strategies that have been developed to identify and prioritize bacterial originating biosynthetic gene clusters (BGCs) of ribosomally synthesized and post-translationally modified peptides (RiPPs). Upon history, they visioned the future of genomics-guided discovery of RiPPs, especially the discovery of RiPPs from dominant, but uncultivated microbes [3].

Zhang and colleagues reported that a phosphate-limited cultivation condition significantly increased the titer of Coenzyme Q_{10} in *Rhodobacter sphaeroides* HY01 by disturbing its energy metabolism and redox potential [4].

The review article by Liu and colleagues focuses on plant Cytochrome P450s. The authors reviewed a number of research hotspots of P450 involving plant natural products biosynthesis, including P450 databases, gene mining, heterologous expression, and protein engineering [5].

The research article conducted by Jakočiūnas and colleagues reports the development of a novel, yeast-based, programmable platform for the biosynthesis of bacterial aromatic polyketides. Using this platform, they were able to detect dihydrokalafungin (DHK), the monomer of actinorhodin from the reconstituted actinorhodin biosynthetic pathway, in the yeast strain [6].

Drufva and colleagues reviewed the potential of using a site-directed mutagenesis approach to enable synthetic biology with engineered modular polyketide synthases. Reviewed and discussed are a number of examples of targeted point mutagenesis to one or a few residues harbored within the PKS that alter domain specificity or selectivity, affect protein stability and interdomain communication, and promote more complex catalytic reactivity [7].

The research article by Tian and colleagues describes a fast and simple solution of diagnosing potential metabolic bottlenecks by a cell-free synthesis system to facilitate the cellular resources rewiring-based microbial cell factory construction. They demonstrated this system by diagnosing the N-acetylneuraminic acid (NeuAc) biosynthetic pathway in *Bacillus subtilis* [8].

Piroozmand and colleagues reviewed recent advances in biosensor development for quick, efficient, and accurate detection of natural products [9].

The review organized by Zhou and colleagues summarizes the commonly used regulatory-rewriting strategies, including regulator engineering, promoter engineering, and employing transposons, signal factors, or feedback regulations for natural products discovery and overproduction in *Streptomyces* [10].

The research article by Gao and colleagues report on establishing a platform of applying multiple orthogonally active serine integrases to assemble and express complex biosynthesis pathways in streptomycetes [11].

The review article by Zhao and colleagues summarizes the development and application of CRISPR based genome editing tools in

Peer review under responsibility of KeAi Communications Co., Ltd.

https://doi.org/10.1016/j.synbio.2020.09.001

Available online 11 September 2020

microorganisms, furthermore, they discuss how to optimize and expand CRISPR tools for more microbes, especially for those industrially important microorganisms [12].

Blin and colleagues updated the sgRNA designer CRISPy-web [13] to CRISPy-web 2.0 [14] (https://crispy.secondarymetabolites.org/), which now is completely compatible with the CRISPR base editor CRISPR-BEST [15] for genome editing of actinomycetes.

I hope that readers find the papers in this Special Issue interesting and inspiring to their own research.

Last, but not least, I would like to thank all the contributing authors, hard-working reviewers, and also editors Prof. Lixin Zhang (Editor-in-Chief), Prof. Zixin Deng (Founding Editor), Prof. Tilmann Weber and Prof. Hal Alper for valuable discussions, as well as Wei Yan from KeAi Publishing for her support for making this Special Issue on “Natural Products” possible.

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