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Editorial

Editorial for "Biointelligent manufacturing in Memorium of Arnold (Arny) L. Demain"

Biointelligent manufacturing is currently at the center of industrial biotechnology. Industrial biotechnology has historic roots dating thousand years back where microbial fermentation was used to preserve foods, make bread and fermented drinks, but has risen to a modern industry. Much of the development into a modern industry was driven initially by production of antibiotics and later by production of food and feed ingredients. In this development, the late MIT emeritus Professor Arnold (Arny) Lester Demain was one of the drivers and is considered one of the founders of industrial biotechnology. His research founds wide applications and he stands as one of the giants in the field of industrial microbiology and biotechnology [1–7].

Arny was born on April 26, 1927 in Brooklyn, NY, USA, and deceased on April 3, 2020 at an age of 92 in Madison, NJ, USA. He first worked at Merck for 15 years after receiving his PhD degree in 1954 from the University of California, USA. Since 1969, he became a full professor at MIT, following his final research and undergraduate-teaching position at the Charles A. Dana Research Institute for Scientists Emeriti (RISE) at Drew University, Madison, NJ from 2002 till 2017. During his 60-year career, Arny has revealed many great discoveries in the field of industrial microbiology and biotechnology ranging from bacteria to fungi, from primary to secondary metabolites, from fermentation industry to microbial theories, from their metabolic regulation to genetics. His major contribution were focused on the biosynthesis and (de)regulation of beta-lactam antibiotics, and the development of many industrial fermentation biotechnology. He published more than 570 papers, 14 (co-)edited books, and is an inventor of 21 USA patents, As a former president of the Society for Industrial Microbiology of USA (in 1990) and member of the US National Academy of Sciences (since 1994), Arny recieved numerous awards in the field of industrial microbiology and biotechnology. Furthermore, Arny was a humorous and wonderful mentor, a nice person and a hard worker for his students and scholars, and loving father for his family. In honor of Arny since his emeritus in 2001 from MIT, "Arny's Army & Friends" (AAF) members, which consist of his students and friends since his retirement in 2001 from MIT, have succeeded and developed his academics and social impacts, and have played a decisive role worldwide in the broad ranges from industrial microbiology and biotechnology to the frontiers in molecular biology, microbial omics, synthetic biology, and systems biology.

In tribute to Arny's tremendous contributions, the journal *Synthetic and Systems Biotechnology* dedicates a Special Issue on the topic "Biointelligent Manufacturing in Memorium of Arnold (Arny) L. Demain".

1. Biography

The eminent Professor Erick J. Vandamme, as former postdoc with Arny's supervision in MIT during 1974 and 1975, generously donates his cordial appraisal as the sole memoir in this collection, in which Arny's lifespan, scientific achievements and impact for the global talents are reviewed in a personal writing style [1].

2. Biointelligent manufacturing of natural products

To achieve highest yield and titer with least cost of natural product, biointelligent manufacturing has been steadily and deeply employed, e.g. the "5 M" strategy for avermectin fermentation [8]. The first step for the biointelligent manufacturing of natural products is to find novel natural products and/or broaden the native producer sources. In this collection, Lu et al. report identification and bioactivity assessment of the aliphatic unsaturated alcohols, fusariumnols A and B, from a pathogenic fungus *Fusarium proliferatum* strain 13294 [9]. Sugar uptake capability is greatly decreased during secondary metabolite biosynthetic period in antibiotic producing *Streptomyces*. Through screening both genomic and transcriptomic levels in milbemycins producer *Streptomyces bingchenggensis*, Jin and co-workers characterize two ATP-binding cassette transporters TP2 and TP5 for sugar uptake. By fine-tuning their expression level, the yields and titers of 3 macrolide biopesticides, milbemycins, avermectins and nemadectin, were significantly improved in their *Streptomyces* producers, which can be an effective strategy for *Streptomyces* metabolic engineering [10]. Yu and collaborators reveal that 17 genomic neutral sites for gene integration are screened for metabolic engineering of methylotrophic yeast *Ogataea polymorpha* using CRISPR-Cas9 technique. The case study using neutral sites NS2 and NS3 for integrating fatty alcohol synthetic pathway genes also sheds light on such screening method feasible for other eukaryotes [11]. For complex natural product biomanufacturing, both traditional and update methods are reviewed by Park and co-workers. In this context, the native and heterologous systems for natural product biosynthesis are compared, and a novel cell free production systems are also introduced with a test case of erythromycin biosynthesis [12]. To express and library screen the intact fungi biosynthetic gene clusters (BGCs) in heterologous hosts such as *Saccharomyces cerevisiae,* Liu et al. discuss the development and prospect of a new strategy on library screening of fungal BGCs in yeast without refactoring [13].

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3. Enzymes and proteins

Enzymes and proteins are essential components for host live and metabolic biosynthesis. By expanding the 5-membered thiazole ring of penicillins to generate the 6-membered thiazide ring of cephalosporin, deacetoxycephalosporin C (DAOC) synthase (DAOCS, or expandase) is a vital enzyme and the rate-limiting step in the biosynthesis of cephalosporin. Although DAOCS in the fungus *Acremonium chrysogenum* is characterized as a bifunctional enzyme of both ring expansion and hydroxylation, in bacteria the two separate DAOCS and deacetylcephalosporin C hydroxylase catalyze ring expansion and hydroxylation subsequently. Niu et al. highlight the source and function of DAOCS, enhancement of the conversion rate of penicillins to DAOC via DAOCS modification, their crystallography features and the active site prediction, as well as application perspective [14]. Prenyltransferase (PTase) are indispensable in prenylated compounds biosynthesis via transferring isoprene unit(s), Chen and Abe give some examples of microbial soluble aromatic PTases for prenylation modifications to create new unnatural prenylated compounds [15]. Similar to glycoside hydrolases or glycosyltransferases, disaccharide phosphorylases (DSPs) are modular enzymes which produce active homo-oligomers with attractive properties, especially specific disaccharides. Sun and You summarize the properties and classifications of known DSPs and their applications for glycoside products [16]. Protein chemical modifications, such as unnatural amino acid incorporation by genetic coding expansion, enzymatic tailoring reactions and recognition-driven transformations, are imperative means for clarifying chemical and biological functions of enzymes and proteins. Some recent research progress are reviewed by Naowarojna and colleagues with certain metalloenzyme examples [17].

4. Biotechnological methods and tools

The rapid progresses of various biotechnological approaches, such as molecular biology, bioinformatics, omics and synthetic biology, etc., have greatly driven the development of the biointelligent manufacturing. Finally, in this collection, some new methods are also introduced besides the tools mentioned above [10–12]. Sun et al. report the establishment of scarless gene deletion and its first application based on uridine auxotrophy in *Acremonium* species, with the potential in assistance of sequential genetic analysis of filamentous fungi [18]. Plant cytochrome P450s decisively function the diversification and modification of plant natural products. Wang and colleagues establish a plant P450 database (PCPD: http://p450.biodesign.ac.cn/), in which the sequences, structures and functions of the 181 plant P450s are included, and a web service based on a high-resolution P450 structure prediction process (PCPCM) and a ligand docking process (PCPLD). This work also introduces a universal strategy for the mining and functional analysis of P450 enzymes [19]. Synthetic biology is currently a raising and promising tool for biointelligent manufacturing. The review by Xiang et al. presents the workflow to construct chassis cells for the aromatic pollutants degradation and provide a suggestion to design microbes with synthetic biology strategies in this area [20].

Finally, we thank all contributing authors for making this special issue on "Biointelligent Manufacturing in Memorium of Arnold (Arny) L. Demain" possible, and also the reviewers for their time and constructive comments throughout the reviewing process to improve the manuscripts. The big support and valuable suggestions from Prof. Lixin Zhang (Editor-in-Chief), as well as Dr. Wei Yan from KeAi Publishing for her hard work in supporting this special issue. We hope that readers find these articles interesting and inspiring to their own research.

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Qiang Gao*
Key Laboratory of Industrial Fermentation Microbiology of Ministry of Education, College of Biotechnology, Tianjin University of Science and Technology, Tianjin, 300457, China

Jens Nielsen
BioInnovation Institute, Ole Maaloes Vej 3, Copenhagen N, DK2200, Denmark

* Corresponding author.
E-mail address: gaoqiang@tust.edu.cn (Q. Gao).