

Preface

Currently, large-scale production of chemicals, fuels, biomaterials, and pharmaceutical products from renewable materials draws on biological systems and processes primarily based on microbial, mammalian, and plant cells. With a few exceptions, enzymes have been mainly used as biocatalysts for biotransformations to produce specialties and intermediates. While these bioproduction systems have many important advantages compared to chemical production processes, indeed these have contributed greatly to the health and welfare of human beings and to the protection of our environment, they have several inherent limitations. First, the product yield is often limited (maximum about 50 % by weight of substrate used even for primary products such as ethanol) due to the underlying biochemical principle of coupled oxidation and reduction of the substrate: much of the substrate is released as CO₂. Second, microorganisms are evolutionarily optimized for their growth and maintenance, not for the formation of a special product which we desire to have. Despite the tremendous advances in biological fundamentals and bioengineering techniques, it is today still difficult to precisely and predictably manipulate a microorganism (e.g., by metabolic engineering or synthetic biology) for the purpose of bioproduction. In addition to the complex regulation mechanisms at different molecular levels, a major challenge and barrier is the cell membrane or cell wall which prevents the accumulation or secretion of desired products. Adding to the fact that cellular production processes take place almost always in water, we have normally a much diluted “aqueous soup” as the product from a typical bioproduction process, leading to high energy and investment costs for the product recovery. Furthermore, complex substrates such as hemi or lignocellulosic materials which represent the most abundant and cheap renewable substrates can still not be efficiently used in present bioproduction systems using single microorganisms. This is one of the obstacles for the realization of a bio-based economy with the aim to move away from a fossil-based one. There are therefore needs to look for alternatives or new concepts of bioproduction systems. One of the new and alternative bioproduction systems is the cell-free biosynthesis which could, in principle, overcome many of the major constraints of present bioproduction systems. In general, the de-coupling of biosynthesis reactions or pathways from the cellular machinery can allow for much higher product yield and thus reduce by-product or waste generation. The biosynthesis could be more easily manipulated and also carried out in nonaqueous solutions. Biosynthesis outside the

cells could provide completely new possibilities which are unthinkable with the present bioproduction systems.

In this volume, eight contributions are lined up to review and illustrate some of the fundamental issues, tools, promises, and applications of cell-free bioproduction systems. The article of Loeffler et al. describes the latest developments in peptide synthesis in an array format and presents a novel synthesis method using a microelectronic chip printer. This technology represents a so-called “printing bioproduction system” and allows the precise and massive production of artificial molecules or molecular building blocks. Bornscheuer illustrates the concept of protein engineering and its potential application for novel bioproduction systems. Jandt et al. gives insight into molecular strategies and modeling approaches for understanding and designing compartmentalization and metabolic channeling in multienzymatic systems for efficient biosynthesis, also in the context of in-vitro biosynthesis. The article of Ardao et al. addresses multienzymatic reaction systems from a more technologically oriented point of view, including process design aspects, strategies of co-immobilization of multienzymes in nano/micro-sized materials. It also highlights recent developments in applying multienzyme microreactors for biosynthesis. Rupp gives an overview on recent developments in design and modeling of molecular circuits with cell-free protein synthesis technology and for in vitro biosynthesis. Furthermore, he illustrates the need and perspectives of developing novel reactor concepts for cell-free biotechnology. The article of Stech et al. presents recent advances for cell-free synthesis of glycoproteins, membrane proteins, and fluorescently labeled proteins. These are difficult-to-express proteins and require organelles or microsomal vesicles as functional modules for translocation and post-translational modification. This work builds a bridge to synthetic and chemical biology. The article of Zhu et al. reviews the current status of cell-free technology and its applications in the production of electricity and bioenergy (hydrogen, alcohols, and jet fuels). They also address issues related to the high costs and low stability of enzymes and cofactors as well as compromised optimal conditions for enzymes from different sources. These are often argued as critical issues against cell-free biosystems as means for large-scale biomanufacturing. The last article of this volume by Krauser et al. presents a new bioproduction system as a middle-way between living cells and cell-free systems, namely tailored and permeabilized cells for multienzymatic biosynthesis. Practical examples are described to use this probably more cost-efficient production system for the synthesis of phosphorylated carbohydrates, sugar nucleotides, and polyketides.

The reader may have noticed that the majority of the authors of this volume are from Germany. Among other reasons, this may reflect the desire and efforts of the German government to develop the so-called “Next Generation Biotechnological Processes” in its research program “Strategy Process—Biotechnology 2020+.” Most of the authors from Germany are involved in this long-term research program. Indeed, many of the new bioproduction systems presented in this volume may really need a long-term research and development to be made mature for large-scale biomanufacturing. This long-term endeavor is, in my opinion, both

timely and economically necessary in view of the limitations of present bioproduction systems and the large hope for a successful bioeconomy. It is also scientifically both highly interesting and challenging. Of course, I should mention that cell-free biosynthesis is only one type of the new bioproduction systems under development. The upcoming era of the synthetic bio(techno)logy will certainly result in new bioproduction systems with synthetic cells, prototype cells, self-reproducing organelles, or even vesicles, which may have unique properties and advantages. The substrate basis and energy supply systems may also completely change, i.e., from sugars move to CO_2 , H_2O , light, and electricity. We are living in an exciting time for developing new and efficient bioproduction systems for the sake of human beings and our environment.

I cordially thank the authors for their excellent contributions and hope that this volume will inspire the future development of new bioproduction systems.

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An-Ping Zeng



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