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Brief Note on the Development of Biotechnology

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Summary

Biotechnology, with the main applications in food and nutrition, dates back to the early times of mankind. In the recent decades the progress in natural sciences, mathematics and computer science has led to a new branch termed molecular biotechnology, which finally developed as an autonomous scientific discipline. The field of biotechnology, in the past generally empirically driven, now largely benefits from molecular biotechnology by improved systems, knowledge and understanding. Thereby, compliance with the recently published initiatives of the regulatory authorities to accelerate the approval process for the manufacturing of biopharmaceuticals can be gained.

Key words: molecular biotechnology, biopharmaceuticals, PAT, QbD

Introduction

The benefit of biotechnology for the welfare of mankind has a long history. Biotechnology commonly defined as the scientific application of microbiology and biochemistry in close connection with chemical, process and plant engineering for the utilisation of biological phenomena on technical and industrial scale has experienced a substantial change during the recent decades. For a long period food technology was the main area of application. Nowadays, biotechnology significantly contributes to the areas of health, nutrition and environment. Due to the high impact of biotechnology on the welfare and the economy of human society, biotechnology and health are even regarded as the bearers of the 6th Kondratieff cycle, thus representing a landmark of scientific and economic development (*1–4*).

In the context of the special edition of the journal it is important to note that the work life of Prof. Mildner largely corresponds with the remarkable development of biotechnology.

Evolution of Biotechnology

As mentioned, in the past the main area of biotechnology was food technology. Due to the impact of nutrition on health in former times, biotechnology was closely associated with traditional medicine. However, the less explored knowledge of nutritional science often resulted in hazardous adverse reactions or even disease caused by effects of food. In the last century the artisanal craft processes of food technology were more and more mechanised, which was the beginning of industrial food production. In parallel, at the end of the 19th century, organic chemistry gained ground in the synthesis of pharmaceuticals over compounds extracted from natural resources. Among others, the well known acetylsalicylic acid (ASA) or the sulphonamides are typical examples. However, the discovery of penicillin by Fleming in 1928 brought a paradigm change in the application of pure chemical drugs to biopharmaceuticals. The following efforts to develop production of penicillin and other antibiotics on industrial scale can be seen as a cornerstone in pharmaceutical biotechnology-based manufacturing (for details refer to Buchholz and Collins (*5*), and Hulse (*6*)). The specific requirements of penicillin production connected with pure cultures on a large scale introduced the application of engineering principles and skills. As an example, in the beginning *Penicillium* sp. was cultivated in milk bottles prior to the construction of bioreactors. Process development and construction of

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plants on industrial scale was strongly forced by the high requirement of antibiotics due to the Second World War. Interestingly, Prof. Mildner graduated in organic chemistry during that time and also got involved in a pharmaceutical company.

In the context of biotechnology as the carrier of the 6th Kondratieff cycle, it is worth mentioning that a fundamental attribute of such long-term cycles is the convergence of a series of mutually complementing technical and methodological innovations leading to complex systems. The key disciplines of modern biotechnology are biological sciences, (bio)chemistry, informatics, mathematics, and engineering science. Each of these showed significant progress in the recent decades. In brief, biological sciences have been strongly stimulated by molecular biology, in particular by the discovery of the structure of DNA, gene cloning and the significant progress in bio-analytics such as genome sequencing and development of high throughput -omics platforms. The advances in molecular biology have been greatly supported by the rapidly growing capabilities of computer science (*7*). To cope with the wealth of data, bioinformatics adopted a series of methods to store, retrieve, organize and analyze biological data. The availability of such comprehensive data sets has led to a change from 'hypothesis driven' to 'data driven' investigations using statistical modelling. Moreover, the comprehensive and partly quantitative data sets provide the basis for mathematical modelling and simulation of pathways and regulatory networks. The progress in computer science also provided the basis for advanced process control and automation. At this point it needs to be said that the current high level of biotechnology is to a major part the result of inter- and transdisciplinary collaboration of many open-minded scientists from the different fields. It needs to be emphasized that often work had to be performed under stringent economic conditions. At this point the value of Prof. Mildner's contribution to research and education also has to be honoured.

Following the progress in science within the recent years, biotechnology has undergone a change. In addition to the traditionally defined utilisation of biological phenomena for the production of goods on technical scale, recently the field has been extended to 'molecular biotechnology'. In brief, molecular biotechnology encompasses a broad spectrum of laboratory techniques such as molecular biology, biochemistry, microbiology, immunology and cell biology applied for targeted modification of cellular systems in the production of therapeutic molecules and/or biocatalysts used in the area of white biotechnology. Currently the major part of products is applied in the health area. In addition to the biosynthesis of specific molecules, the use of modified cells in cell-based therapies is an increasing field of application in personalised medicine. A strong impetus to molecular biotechnology in direction of health applications was triggered by the human genome project (HUGO), which started around 1990. In parallel, in the wake of the human genome project, the capabilities and the performance of the analytical equipment advanced significantly. The knowledge of the human genome offers new possibilities in diagnosis and therapy. Moreover, it opens new insights into the complexity of cellular systems for targeted treatment of diseases. Interestingly, based on the improved understanding of cellular regulatory networks, recently medicinal chemistry approaches have been investigated more extensively as new drugs lead to targeted interaction with specific pathological entities. Such therapeutic concepts might result in a substantial reduction of costs of goods (COGs).

As a whole, molecular biotechnology encompassing biochemistry, molecular biology and cell biology, bioinformatics and mathematical modelling has evolved into a new scientific discipline in the framework of life sciences (*5*).

Impact of Molecular Biotechnology on the Production of Biopharmaceuticals

The observability and controllability of biopharmaceutical production processes is generally impaired by the complexity of the cell factory and the insufficient insight into the synthesis processes. Therefore, in the past, and due to the usually long life cycle of biopharmaceutical production processes as a consequence of stringent regulatory and intellectual property issues even in present times, the upstream processes are run under a tight control regime of a few state parameters. The required product quality and efficacy are assured by in-depth analysis of the product afterwards. Such an approach 'quality by quality control' does not comply with modern process control strategies which are based on timely measurements and interventions in the course of the production process. Based on the advances in modern biotechnology offering better insight into the cell factories and improved process understanding, the regulatory authorities started an initiative to transform and facilitate the acceleration of the marketing authorisation approval process of biopharmaceuticals. The key requirements are to improve process knowledge and understanding to lower the risk of application of the specific drug. The key elements of this initiative are Process Analytical Technology (PAT), Quality by Design (QbD) and the definition of the Design Space (*8*). PAT is focused on advanced timely monitoring, the QbD concept aims at understanding of the production process in accordance with the knowledge of the risks involved in manufacturing. The Design Space defines valid operation parameters to meet the product quality attributes within a solution space. Detailed definitions are documented in the guidelines issued in the recent years by International Conference on Harmonisation (ICH): 'Pharmaceutical Development Q8 (R2)' (*9*), 'Quality Risk Management (ICH Q9)' (*10*), 'Pharmaceutical Quality System (PQS) (ICH Q10)' (*11*) and 'ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities)' (*12*). The guidelines strongly emphasize the benefits of increased understanding and knowledge of the manufacturing process to lower the risks and facilitate the approval process. In addition, the supported risk-based regulatory decisions are the basis for improvements of the manufacturing process within the approved design space. Hence, the envisaged reduction of post-approval submissions and real-time quality control will result in reduced end-product release testing and will shorten the time to the market as well.

However, thus required increase of process knowledge is impaired by the low observability of cellular processes in real time due to (*i*) the lack of sensors reflecting the physiological state of the culture, (*ii*) the complexity of the biochemical reactions involved in the biosynthesis processes, and (*iii*) the constraints in obtaining any signal from inside the cell. In the recent years, progress in the following areas has enabled substantial improvement of bioprocess monitoring capabilities: a) biochemical/molecular biology-based off-line analytics is subject to a dramatic improvement, *e.g*. –omic technologies, mass spectrometry, sequencing, *etc*.; b) new on-line analytical devices exploiting chemophysical features appeared on the market, *e.g*. dielectric spectroscopy for the determination of biomass, multiwave 2D fluorescence to acquire *in situ* emission, and acquisition of volatile organic compounds in the bioreactor exhaust gas by proton transfer reaction mass spectrometry (*13,14*); c) data mining and data compression using computer-based statistical methods to extract key process variables (*15*); and d) statistical modelling to predict process variables that are not directly measurable in the required time frame by generating correlations between on- and off--line data sets (*16*).

Hence, the application of a comprehensive monitoring platform provides a readout of physiologically significant variables such as active biomass and/or product concentration in real time, which in turn can act as new set points for advanced process control regimes.

To sum it up, molecular biotechnology played and still plays a pivotal role in the fruitful development of biomedical research and therapy and has also led to a paradigm change in biopharmaceutical manufacturing.

Conclusion

The progress in natural sciences, mathematics and computer science was heavily instrumental in the transformation of biotechnology to an autonomous scientific discipline – molecular biotechnology – which nowadays exists in parallel to the traditional technology-driven biotechnology. Remarkably, traditional biotechnology also takes advantage from the progress in mathematics, statistics and specific areas of natural sciences to improve process knowledge and understanding. Thereby, the interaction of biotechnology and molecular biotechnology largely contributes to the efficient and economic manufacturing of biologics. Analogous approaches have already been implemented and will be further applied in food technology.

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