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Editorial

The Future of Biotechnology

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Biotechnology has been used for many centuries – ever since the first humans produced alcoholic beverages, made bread and cheese and preserved food they utilized concepts of biotechnology. Very little changed in the way these 'biotechnological' approaches have been employed until the discovery of DNA as the tractable material of inheritance in the last century. However, it still should take several decades to develop the tools to establish a profit-making industry based on biotechnology. The accounting agent Ernst & Young scanned the international biotechnology market and found that 2009 was the first year in which biotech hubs achieved a collective profit [1]. So what is in store for the Biotechnology industry in the future?

There is no doubt that biotechnology is one of the developing key industries, which will have almost unforeseeable effects on everybody's lives. In general the biotechnological industry can be divided in manufacturers of high volume, low price (HVLP) products and low volume, high price (LVHP) goods. The first category comprises components, which can be produced in large quantities, but do not have a very high market value, e.g. citric acid, ascorbic acid, ethanol, to name only a few. LVHP products, on the other hand, are goods like specific antibodies, growth factors or biopharmaceuticals, like vaccines, which can only be manufactured in low amounts with high production costs. Many companies in the biotechnology sector are now focusing on this very lucrative market and therefore it is worth exploring the conditions for sustainable growth in this area.

In general, LVHP goods are manufactured utilizing living cells, either prokaryotes or eukaryotes. Certain products, however, can only be produced in eukaryotic cells, like antibodies, due to the requirement for post-translational modifications. The current approach here is to utilize well-established cell culture systems, which are suitable to synthesize the desired products. Compared to prokaryotic production systems, however, these eukaryotic cell factories are usually far less efficient in generating high yields. One approach therefore is to investigate ways to increase the yield and productivity of these cell culture systems in a rational way. While upstream processing focusses on optimizing growth conditions and the development of suitable cell lines, downstream processing deals with the efficient purification and quality analysis/assurance of the manufactured products. Currently there are only a few well-established cell lines suitable for the large-scale production of such LVHP products, like Chinese Hamster Ovary (CHO) cell or Mouse myeloma (NS0) cell lines.

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Rational cell engineering aims to increase the quality and quantity of the manufactured products by developing improved cell lines. Previously the selection for improvements has been carried out on a trial and error basis: cells that produced high levels of the desired product were positively selected and kept, while low-producing lines were discarded. Little or no understanding of the underlying biological and molecular processes was applied in this selection. However, with the increasing availability of new tools a more informed process is now possible. Most of these tools developed in the past decade aim to understand the biological make-up of cells by employing high-throughput (HT) approaches. For example, the HT of DNA sequencing allows the analysis of the genome of a specific cell line (genomics), RNA microarrays give information about the different types of mRNAs in a cell (transcriptomics), HT analysis of the entire protein contents shows the individual protein species present in the cell (proteomics). The information that these –omics approaches provide can be very useful for a detailed understanding of the cell factories and hence their improvement for the manufacturing of desired products.

A key technique in this arsenal of methods is the efficient sequencing of whole genomes through HT DNA sequencing. While the complete sequencing of the human genome (3 x 109 bases) took about a decade and had a price-tag of between 0.5 and 1 billion USD, it can now be done for around $4000 within a couple of weeks [2]. Very recently, Oxford Nanopore Technologies announced a novel approach to HT DNA sequencing, which claims to be able to sequence an entire genome for around $1500 in less than 1 hour, using disposable equipment the size of a USB stick [3]. Transcriptomes can also be analysed by DNA sequencing in a method called 'deep sequencing' [4]. For this purpose all the mRNA molecules in a cell are converted into cDNA, which then is sequenced in an HT DNA sequencing approach. Mass-spectrometry analysis of the proteome now

allows the tracking of several thousands of proteins at the same time. The analysis of the entirety of metabolic compounds is facilitated by new approaches in Nuclear Magnetic Resonance [5]. These novel techniques therefore allow an incredibly detailed analysis of cells used in the manufacturing process.

One of the biggest problems with the generated data is to understand how these results affect the biology of a cell. Scientists can easily identify the number of copies of a given gene or the arrangement of certain DNA segments within the genome, but still be unable to comprehend the effects on the production pipeline of a specific antibody. Our current knowledge of the underlying biochemical and cell biological processes and how they are interconnected is at the moment too limited. However, getting more data will certainly overcome this problem, thus allowing scientists to develop a thorough understanding of the individual biological components and the way they interact with each other in biological pathways, almost like electronic engineers understand how electronic compounds work for example in a PC. In this case, a considerable gap exists between our knowledge of the biological interactions and the technology.

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Another and potentially even bigger problem is that the aforementioned techniques produced incredible amounts of data. The sequencing result of a genome can easily amount to Terabytes of stored information, and so can the analysis of transcriptomes, proteomes and metabolomes. A hitherto unsolved problem is how these data can be stored, shared and analysed. Again, a considerable gap exists between knowledge and technology, but this time it is the technology lagging behind the knowledge. It is very clear that new technologies have to be developed to compress the data to allow for efficient storage and sharing. We need new algorithms for the analysis of the data – for example the comparison of 10,000s of whole human genomes is currently not possible. How can these enormous amounts of data be visualized and correlated with the underlying biological processes?

It is very clear that the century of biotechnology has just begun, but already its impact can be envisaged: production of specifically manufactured biopharmaceuticals for personalized treatment of individuals is now within the realm of the possible. A thorough understanding of biological processes involved in the onset of cancer, diseases and ageing is feasible. However, what is required now is an interdisciplinary approach to further develop the methods to utilize all the generated data. If these problems can be solved then biotechnology will revolutionize our future.

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