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Viewpoint

Embracing Nature's Catalysts: A Viewpoint on the Future of Biocatalysis

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Enzymes are nature's catalysts that are designed to accelerate specific reactions up to 10^6 times with high selectivity.[1] The enormous potential of enzymes as catalysts for organic synthesis has been recognized very early, as nicely described by Stanley Roberts in the late 90s.[2−4] Thus, these have become an increasingly attractive alternative to conventional chemical catalysts. The field experienced a real boom with the necessity to produce enantiopure compounds. Initially, mainly lipases and esterases were used for the synthesis of chiral compounds. However, the portfolio of available biocatalysts was soon expanded to include nitrilases, ketoreductases, and transaminases, etc.[5,6] These biocatalysts made essential building blocks for pharmaceutical syntheses such as amines and alcohols accessible. An important step forward was the implementation of directed evolution.[7−9] Directed evolution in the laboratory facilitated the adaption of enzymes to technical challenges such as substrate scope, selectivity, or process stability. While directed evolution showed remarkable results, a substantial amount of experimental efforts is needed for biocatalyst optimization. Many examples have also proved that integrative strategies of computational methods with directed evolution outperformed individuals. An increasing number of computational methodologies and tools have been developed to assist in the faster identification of suitable enzyme starting activities and the design of smaller and smarter enzyme mutant libraries.[10−12] Recently, Janssen and Wu computationally redesigned a highly selective aspartase, which they claim "is a notoriously difficult candidate as a starting point for evolution", for the hydroamination of different acrylates.[13]

Evolved enzymes are not only used for individual reactions but also for cascading several enzymes or incorporating newly developed enzymes into metabolic pathways (synthetic biology).[14−16] In the last 20 years, many companies realized the potential of applying selective enzymes to manufacture chemicals, active compounds, or generate entirely novel materials. In this respect, biotechnology/biocatalysis groups were implemented in industrial research departments, and companies were founded to push the technology even further. Simultaneously, in academia, new research centers with a cross-disciplinary structure have been established. Looking at this research field from this perhaps somewhat academic point of view, it looks very promising. Despite considerable progress, the scientific breakthroughs and possibilities to manufacture all kinds of molecules are currently not reflected in the market. In the chemical industry, there is pressure to achieve economic success and to live up to the expectation that had been placed on it. Interestingly enough, efficient, economic processes very often show also an improved overall eco-balance. From companies or even investors, some obstacles become apparent that dampen the current and noncurrent market success. Scientists in the industry are almost in a "depressed mood" about the question: What should we do to become more successful and with which products can we aim to have the right impact on the market?

In this viewpoint, I will discuss current problems and challenges of transferring biocatalysis into processes to manufacture chemical compounds. I will mainly focus on the chemical industry, but I will also address issues that apply to both the chemical and pharmaceutical industries. I would also like to point to recent reviews on the scientific and future developments of biocatalysis in the pharmaceutical industry.[17,18] I will further evaluate possible scientific and technical developments that indicate on how to overcome these challenges. Biocatalysis is regarded as a key technology for the coming years. With this in mind, I hope that you will find this viewpoint to be a practical and useful guide toward a prosperous future of applying enzymes as catalysts.

■ WHAT ARE THE TOP THREE CURRENT CHALLENGES OF BIOCATALYSIS?

Talking to many scientists in different industries as well as listening to plenary discussions at meetings it became evident that transferring reactions catalyzed by enzymes into industrial processes faces three major challenges to be successful (Figure 1).

Performance. When considering biocatalysis alongside heterogeneous catalysis, although some overlap in operating conditions such as pH, temperature, and pressure is possible between reactions, in general, with heterogeneous catalysis, space-time yields (STY) between 1 and 10 kg L^{-1} h^{-1} are obtained. In comparison, biocatalysis frequently reaches STYs in the range of 0.001−0.3 kg L^{-1} h^{-1}. Thus, the challenge in industrial biocatalysis is to identify and to engineer the perfect enzyme for the synthesis of chemical products and to implement

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