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New trends in industrial biocatalysis

1. Preface

The "manufacture and modification" of molecules in nature are catalyzed by enzymes with exquisite selectivity, unparalleled rate acceleration and under "mild" reaction conditions. Nowadays, enzyme-catalyzed synthesis is an attractive and eco-friendly alternative to the traditional multi-step and contaminating chemical processes. In addition, the use of enzymes as industrial catalysts can thus provide novel and straightforward synthetic schemes and suitable and efficient methodologies for developing sustainable industrial processes (Fryszkowska and Devine, 2020; Wu et al., 2021).

A biotechnological alternative to such chemical processes involves enzymes that bypass several of the chemical steps, which can be accompanied by cheaper production. For instance, the reduction of multistep chemical processes into a one-pot, one- (or several)-step biotech or chemo-biotech process can lead to a very significant reduction of manufacturing costs (Fernández-Lucas and Camarasa, 2018; Wohlgemuth, 2021). As a result, high-quality products can be achieved through an economically and technologically competitive and sustainable way, and several companies have thus optimized or even replaced existing processes.

Moreover, from an environmental point of view, enzymatic reactions are more compliant with the principles of greener and more sustainable chemistry, in terms of atom economy, resources and energy efficiency, that will be translated into lower energy consumption, reduction of industrial pollution and thus, in an overall, lower-carbon footprint. In this respect, industrial biocatalysis complies with most of the 12 principles of green chemistry, showing remarkably increased atom economy, reduced energy consumption, biocatalyst recycling and reduction in the use of hazardous solvents and dangerous reagents (Sheldon, 2012).

This special issue focuses on selected hot topics of biocatalysis and biotransformations in industrial biocatalysis, such as microbial cell factories, enzyme immobilization, rational design of biocatalysts, directed evolution or biocatalysis in non-conventional media, among others, and aims to dip into the current tendencies in industrial biocatalysis.

To this end, a total of ten reviews written by world-leading experts were compiled in order to show the state-of-the-art and future trends in industrial biocatalysis.

In the enzyme immobilization section, Arana-Peña et al. (2021) report an overview about enzyme co-immobilization, discussing the advantages but also the drawbacks of enzyme co-immobilization, focusing on recent strategies to overcome some of the inherent problems associated with co-immobilization. In another interesting review, the authors dip into recent findings in the development of innovative nanobiocatalysts and their application in biocatalytic transformations (Gkantzou et al., 2021). Moreover, the effect of nanosupports on the biocatalyst's structure and catalytic performance is also described. Finally, the same authors highlight in their article the use of nanobiocatalysts in multi-enzymatic processes, with illustrative examples about their industrial implementation in various types of batch and continuous-flow reactor systems (Gkantzou et al., 2021).

Regarding bioprocess engineering, two different reviews tackle the importance of medium engineering and protein engineering in the industrial implementation of bioprocesses. On the one hand, Xu et al. (2021) offer an interesting overview concerning the potential of ionic liquids in biocatalysis, emphasizing their unique operational characteristics (namely, nonvolatility, inflammability and tuneable properties regarding polarity and water miscibility behaviour) compared to organic solvents. The authors also provide illustrative examples of biocatalytic production of fine chemicals in ionic liquids. On the other hand, another interesting review (Hobisch et al., 2021) describes the recent trends in the use of peroxygenases for selective oxyfunctionalisations, including an exhaustive description concerning the different protein sources, the application of protein engineering strategies for expression, substrate scope, activity and selectivity, and the effect of immobilization on enzyme stability and their use in low water media.

This previous article also serves as a nexus with the next section, which focuses on the use of oxidoreductases in biocatalytic reactions. In this sense, many different reports have provided detailed comments and perspectives about different oxidoreductases, such as flavoprotein monooxygenases (FMPOs), carbohydrate oxidases (COs), *N*-oxygenases (NOs) and unspecific peroxygenases (UPOs). Interestingly, the role of FMPO in a diverse set of chemo-, regio- and enantioselective oxyfunctionalization reactions was addressed by Paul et al. (2021), including a detailed explanation about historical FPMO classification, mainly based on protein folding and electron donor specificities. Additionally, detailed examples about the potential of FPMOs as biocatalysts for oxygenation reactions, as well as recent engineering strategies for the improvement of the operational stability of FPMOs are also included. In another exciting article, Savino and Fraaije (2021) exhaustively describe the extensive repertoire of COs, highlighting the evident variations among the different COs regarding sugar specificity and selectivity of the oxidation site. Moreover, detailed comments about reaction mechanism, the engineering of novel COs, and some biocatalytic applications of COs in the industrial oxidation of carbohydrates, and as efficient tools for biomedical diagnosis and food preservation, are summarized (Savino and Fraaije, 2021). Nóbile et al. (2021) performed a detailed perspective about oxidation of amino to nitro groups catalyzed by NOs, but also in

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obtention of less oxidized N-O compounds (*e.g.,* hydroxylamine or nitroso derivatives). Moreover, the authors also addressed the use of NOs, as enzymes or whole cells, as oxygenation biocatalysts for the greener production of high added-value nitro compounds. Last but not least, in this section of the special issue, Aranda et al. (2021) give an updated perspective about aliphatic oxyfunctionalization reactions catalyzed by UPOs, including detailed comments about the structural determinants which lead to these unusual activities.

In the last section, the importance of transglycosylation reactions in biocatalysis is discussed in two interesting reviews (Del Arco et al., 2021; Mészáros et al., 2021). In the first article, the authors analyze the potential of 2′-deoxyribosyltransferases (NDTs) as industrial catalysts for the synthesis of nucleoside analogues. To this end, recent examples about the use of NDTs in mono- and multienzymatic reactions, but also in chemo-enzymatic processes and in in-flow processes, were included. Additionally, the potential of extremophilic NDTs, protein engineering, and immobilization strategies in biocatalyst stabilization, were addressed. Moreover, the authors include a detailed analysis of recently granted patents, with specific focus on industrial synthesis of nucleoside analogues. Finally, Mészáros et al. (2021) display a recent perspective about the synthetic application of glycosynthases as industrial catalysts for the production of well-defined chitooligomers, precious galactooligosaccharides or specialty chemicals. Furthermore, the authors also include detailed comments about the molecular bases for glycosynthase design, shedding light on outstanding questions and bringing to the reader novel perspectives in this field.

In conclusion, the abovementioned reviews present a comprehensive exhibition of the general knowledge and representative frontier developments in the industrial application of enzymatic bioprocesses. The crucial aspects of this field, including comprehensive issues regarding the scale-up of bioprocesses from bench to plant, are also described in the collected articles.

Finally, we would like to thank all the authors, reviewers, and the Editorial Board members of Biotechnology Advances for their considerable contributions to support the implementation of this special research topic, and we hope that the readers will enjoy their work.

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