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Guest Editorial: Biocatalysis and Pharmaceuticals

Mankind's ability to harness the power of biocatalysis dates back many thousands of years as evidenced by records that described the production of beer by the Sumerians. Over the next few thousand years many other uses of biocatalysis were discovered, mainly for the production of food and drinks such as cheese and wine. Yet it took until the 20th century for mankind to utilise biocatalytic reactions for the synthesis of chemical intermediates and active ingredients (1).

Biotransformations are chemical reactions that are catalysed by biological systems such as microbial whole cells or isolated enzymes. Most of the early examples of biocatalysis used wild type microorganisms but advances in genetic engineering in the 1970s allowed scientists to clone and express specific enzymes in organisms that are easily handled and grown in a laboratory environment such as *Escherichia coli* and yeast.

Johnson Matthey has extensive capabilities in terms of enzyme discovery, evolution and manufacture along with a broad range of proprietary enzymes for the effective synthesis of pharmaceuticals and fine chemicals.

Biocatalysts and Chemocatalysts

Biocatalysts – like all catalysts – increase the rate of a reaction by lowering the activation energy and they are not consumed in the reaction they catalyse. Enzymes and whole cell biocatalytic systems display several unique properties. Most importantly, the regio-, chemo- and stereoselectivities of biocatalysts are often much higher than what can be achieved using chemocatalysts as a result of the multiple binding interactions of substrate and catalyst thanks to their complex three-dimensional structure. Biocatalysts are also commonly used in aqueous systems (sometimes with added organic co-solvents to help solubility of apolar compounds) or in biphasic systems. This results in limited use of organic solvents which leads to a reduced environmental impact.

The industrial use of enzymes encompasses a variety of different market segments such as food and beverage, animal feed, detergents, fine chemicals and pharmaceuticals and the overall size of the market was estimated to be US$4.7 billion in 2013 (2). While the pharmaceutical sector occupies a small portion of the overall enzymes market, the recent technological advances in the area of enzyme engineering have led to a much increased interest in the use of enzymes for the production of active pharmaceutical ingredients (API).

From the point of view of the synthetic chemist, it is important to realise that biocatalysis and chemocatalysis are complementary technologies and neither is inherently superior to the other. As they operate under different reaction conditions and they often display a different substrate scope, it is hard to predict which technology will provide the best performance in a given chemical transformation. For example, when high enantio- or chemoselectivity are required, biocatalysis is often the technique of choice, especially when dealing with complex, multi-functional molecules. On the other hand, chemocatalysis can sometimes be the more cost effective approach as it is easier to achieve very high substrate to catalyst ratios and it is often viewed by organic chemists as inherently more familiar technology.

While chemocatalysis can be highly cost efficient it sometimes lacks application flexibility, particularly when there is the need for high hydrogen gas pressure or when small amounts of byproducts cannot be avoided. Biocatalysis on the other hand, often offers a superior product purity (and enantiopurity) at the expenses of a narrower scope of reaction conditions and higher catalyst loadings. Therefore, only by having access to bio- and chemocatalytic solutions and considering

each transformation as a unique case can one unlock the full potential offered by catalysis.

Advances in Technology

Biocatalysis is a field that has benefited tremendously from advances in analytical science, genetic engineering and molecular biology technologies. The development of high resolution X-ray single crystal analysis has enabled researchers to understand the structure of the active site of enzymes (**Figure 1**) which has in turn allowed them to mutate the amino acid sequence of the protein thereby modifying the substrate-enzyme interaction in an effort to increase selectivity or activity. Reduced costs of gene synthesis and gene library synthesis allow for the evaluation of the impact of mutations at target sites more quickly. Additionally, the development of high-throughput material handling and analytics, along with rapid developments in the area of deoxyribonucleic acid (DNA) sequencing has allowed scientists to further optimise enzymes *via* a process called directed evolution. This way the natural mechanisms of evolution are exploited to artificially evolve an enzyme towards new properties such as substrate scope, thermal stability and solvent stability. The ability to modify the activity, selectivity and stability of enzymes *via* this approach has resulted in a number of new applications of biocatalysis in organic synthesis and enabled biocatalytic routes to be much more cost competitive with their chemocatalytic counterparts.

Driven by similar advances in genetic engineering and analytical techniques, the field of synthetic biology has emerged. Applying modern genetic engineering, molecular biology and microbiology techniques it is nowadays possible to design 'biological machineries' that can be utilised for manufacturing complex molecules. From a synthetic chemistry point of view, the ability to combine multiple synthetic steps in a single biological organism as a cascade of reactions is an extremely powerful tool as evidenced by the syntheses of highly complex molecules such as artemisinic acid which is a late stage precursor to the antimalarial drug artemisinin (3) and, more recently, several intermediates in the biosynthesis of morphine and thebaine *via* this approach (4, 5).

In this issue then, enjoy the range of articles celebrating a selection of ways in which biotechnology and chemical catalysis can be made to benefit the industry to create new and better processes, products and intermediates. Few other techniques in the toolbox of the synthetic chemist have seen such a rapid evolution over the last few years and with future advances in the areas of genetic engineering, biology and nanotechnology, we can't even imagine how industrial biotransformation will evolve over the next few decades. Exciting times ahead!

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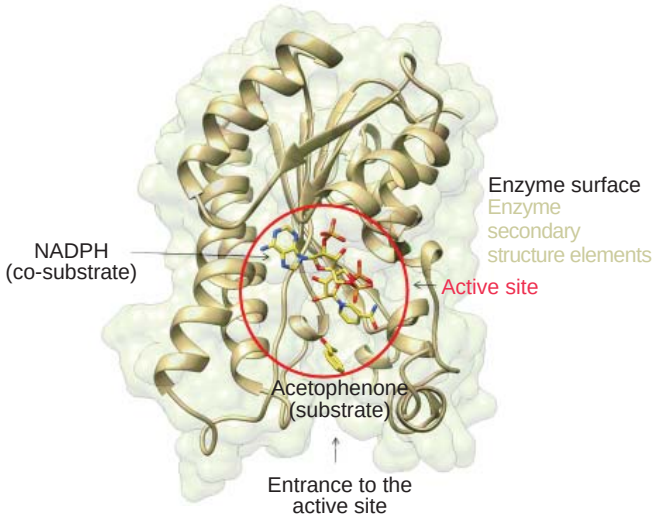

Fig. 1. X-Ray crystal structure of *Lactobacillus brevis* (*R*)-alcohol dehydrogenase © Johnson Matthey

References

1. O. Ghisalba, H.-P. Meyer and R. Wohlgemuth, 'Industrial Biotransformation', in "Encyclopedia of Industrial Biotechnology: Bioprocess, Bioseparation, and Cell Technology", ed. M. C. Flickinger, John Wiley & Sons, Inc, New Jersey, USA, 2010, pp. 1–34
2. S. S. Dewan, "Global Markets for Enzymes in Industrial Applications", BIO030H, BCC Research, Massachusetts, USA, 2014
3. D.-K. Ro, E. M. Paradise, M. Ouellet, K. J. Fisher, K. L. Newman, J. M. Ndungu, K. A. Ho, R. A. Eachus, T. S. Ham, J. Kirby, M. C. Y. Chang, S. T. Withers, Y. Shiba, R. Sarpong and J. D. Keasling, *Nature*, 2006, **440**, (7086), 940
4. K. M. Hawkins and C. D. Smolke, *Nat. Chem. Biol.*, 2008, **4**, (9), 564
5. K. Thodey, S. Galanie and C. D. Smolke, *Nat. Chem. Biol.*, 2014, **10**, (10), 837

