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The Current State of Biocatalysis

from bitBiome's Dr. Ahir Pushpanath

Chemistry has long been the bedrock of modern industry, shaping everything from pharmaceuticals to consumer goods. For many of the most challenging chemical reactions, catalysts are indispensable—and historically, metal-based catalysts have dominated. They benefit from over a century of additional R&D, resulting in a robust collection of off-the-shelf options for countless transformations. Yet amid this metal-dominated landscape, enzymes—nature's catalysts—have quietly come into prominence in distinct "waves," as described by Prof. Uwe Bornscheur. Each wave has been fueled by the promise that these "biocatalysts" can deliver levels of selectivity, especially enantio- and regioselectivity, that conventional catalysts often struggle to achieve. But that same selectivity can be a drawback: natural enzymes are notoriously substrate-specific, requiring extensive tweaking to accept industrial substrates and to achieve viable product yields under manufacturing conditions.

The most transformative wave arrived with the advent of directed evolution, recognized by the 2018 Nobel Prize in Chemistry awarded to Frances Arnold. This technique has revolutionized how we engineer enzymes, unlocking significant breakthroughs in both academia and industry. A shining example is Codexis's R-transaminase for sitagliptin manufacture, a common type II diabetes therapeutic, which showcased the power of biocatalysis in pharmaceutical manufacturing. Despite these successes, enzyme development remains both costly and time-consuming. Compounding this challenge is a general lack of cross talk among synthetic and protein chemists about biocatalytic possibilities and how to access these new and developing tools.

In practice, qualifying a biocatalyst for a synthetic step starts by screening available enzyme libraries for a suitable "hit." Promising hits are then tested against industrial metrics: can the catalyst maintain performance at scale, hitting 100 g/L product titers for active pharmaceutical ingredients, for instance? How easy and cost-competitive will it be to manufacture the enzyme, which is determined almost entirely by fermentation scale and efficiency. These considerations underscore that if enzymes are to truly be a complementary catalyst technology to metal catalysts in industry, the field must address three critical issues: expanding the range of available enzymes (the toolbox) for increasingly complex synthetic challenges, making enzymes accessible to all synthetic chemists (via off-the-shelf screening kits), and ensuring that any chosen enzyme can be readily optimized for large-scale manufacturing. On top of that, as an enzyme service and product provider, flexible commercial terms are often pivotal in enabling real-world adoption.

At bitBiome, we are addressing these challenges with a three-pillar platform: bit-MAP, bit-GEM, and bit-QED. Each pillar tackles a different aspect of the biocatalytic development cycle—discovery, engineering, and data-driven optimization—while maintaining a seamless integration among them. Our approach is built on single-cell microfluidic genomic sequencing (bit-MAP), which overcomes the limitations of traditional metagenomics. Rather than contending with incomplete gene fragments or misassemblies, we capture entire genomes from diverse microbial communities, amassing a database now exceeding three billion genes. This unparalleled genetic breadth means that we're no longer hunting blindly for an elusive enzymatic needle in the proverbial haystack. Instead, AI-driven computational methods help us hone in on precise targets, guided by the knowledge that our expanded gene collection almost certainly contains that rare, previously undiscovered biocatalyst that we need. And because computation alone can't solve every challenge in enzyme development, we complement our predictions with rigorous AI-driven laboratory evolution and screening with high-throughput automation, ensuring every enzyme we deliver meets stringent criteria for production ease and industrial performance.

It's only a matter of time before technology platforms like ours usher in a new golden age of biocatalysis, one in which enzymes become not just an interesting alternative, but the first choice for industrial synthetic chemistry. By systematically removing the bottlenecks in enzyme discovery, development, and deployment, bitBiome is helping to reshape how the world tackles chemical synthesis.

Further Reading:

Bornscheuer, U., Huisman, G., Kazlauskas, R. et al. Engineering the third wave of biocatalysis. Nature. 485, 185–194 (2012). https://doi.org/10.1038/nature11117

Bornscheuer UT. The fourth wave of biocatalysis is approaching. Philos Trans A Math Phys Eng Sci. 2018 Jan 13;376(2110):20170063. https://doi: 10.1098/rsta.2017.0063. PMID: 29175831.