DEVELOPMENT & APPLICATION OF BIOCATALYTIC REACTIONS THAT ENABLE THE SYNTHESIS OF COMPLEX MOLECULES

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I. Biocatalysis as an enabling technology in organic synthesis.

Small molecules make an disproportional impact on human health as drugs that prevent or treat disease, tools for analyzing biological systems, and probes to manipulate whole pathways and individual biomolecules [1]. This limitless potential can be curbed by the practicality and accessibility of target molecules through modern chemical synthesis [2]. The trend away from natural products in drug discovery [3, 4] illustrates this conundrum, as the synthetic challenge associated with accessing these complex structures outweighs their potent activity and therapeutic potential [5]. Chemical methods that facilitate a desired transformation with precise chemo-, site- or stereoselectivity can allow for more efficient synthetic routes free of protecting or directing groups and unnecessary redox manipulations, thus expanding the practical-to-target molecules [6]. Biocatalytic methods present the opportunity to develop exquisite catalyst-controlled selectivity of enzymes, enabling highly streamlined synthetic routes [7-9]. This is exemplified by nature's ability to make intricate secondary metabolites with potent biological activity such as taxol [10, 11] and vancomycin [12, 13]. It is also possible to expedite access to synthetic molecules through biocatalytic strategies, as illustrated by Merck's five-enzyme, one-pot sequence to access the HIV drug, islatravir, dramatically reducing the step count and increasing the overall yield in the production of this nucleoside drug [14]. Although biocatalysis has been embraced by industrial chemists for the commercial production of pharmaceutical agents, several factors have prevented the broad adoption and implementation of biocatalysis in mainstream organic synthesis, including limitations in the breadth of well-developed reactions, the unknown substrate scope of functionally characterized enzymes, and the perceived incompatibility with multistep, preparative-scale sequences [15].

II. My recent research contributions to directed protein evolution for green chemistry.

My research group seeks to provide synthetic chemists with highly efficient, selective, scalable, sustainable, and well-characterized biocatalytic methods that can be smoothly

implemented into synthetic approaches toward target molecules. Using enzymes from natural product biosynthetic pathways and targeted protein families as a starting point, we elucidate the natural chemical function and mechanism of a given biocatalytic transformation. From this initial benchmark, we use bioinformatic tools, structural analysis, computational modeling, and evolutionary approaches to assemble refined panels of complementary biocatalysts of utility to the synthetic community.

At this meeting, two approaches will be discussed for the construction of complex molecules: (a) using biocatalysts to generate reactive intermediates that can be intercepted by small molecule reagents *in situ*, and (b) employing biocatalysts that execute convergent reactions whereby various monomers can be cross coupled on demand. This work to be discussed builds on previous efforts from my research group focused on the development of biocatalytic oxygenation reactions [16,17] and biocatalytic oxidative carbon-carbon bond formation [18].

III. Outlook to future developments of research on directed protein evolution for green chemistry.

With major advances in the fields of DNA synthesis, directed evolution, DNA sequencing, bioinformatics, and computational modeling of proteins, the potential utility of biocatalysis lies in the hands of chemists. Whether biocatalysis remains underutilized in chemical synthesis, will depend not only on the boldness of chemists willing to use large-molecule catalysts but also on the diligence and creativity of chemists characterizing the function of enzymes and developing novel enzymatic transformations.

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