UNIVERSITY OF DELAWARE

CHEMICAL & BIOMOLECULAR ENGINEERING

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ENGINEERING THE REDOX CHEMISTRY OF LIFE

Over 15,000 NAD(P)H-dependent enzymes discovered in Nature represents a rich yet largely untapped resource for catalyst development, with many of these enzymes outperforming any man-made catalysts. To meet the catalytic needs in efficiently converting renewable resources into fuels and chemicals, we established a range of platform technologies to configure these enzymes: First, we developed multiple ultrahigh-throughput (~109 candidates per round of selection), universal, in vivo selection platforms which use cell growth as an easy readout of NAD(P)H-dependent enzyme's activity. Using these selection platforms, we have achieved, through facile rounds of selection, remodeling of substrate scope, improving electron coupling efficiency, switching the cofactor specificity, and enhancing the thermal stability of an industrially important and complex enzymes. Second, we developed a non-canonical redox cofactor system based on nicotinamide mononucleotide (NMN+), which is a much cheaper alternative to NAD(P) in vitro and operates in an orthogonal fashion to NAD(P) in vivo. We demonstrate that this system can be used to support diverse redox chemistries with high robustness, to specifically deliver reducing power in both whole-cell and cell-free biotransformation, and to shift the redox reaction equilibrium on demand. We developed two growth-based selection platforms to evolve enzymes that can oxidize or reduce NMN+, which allowed deep searching of the protein sequence space that give rise to the general design principles. These technologies will not only enable facile control of redox reactions in Nature, but also pave the way for readily expanding what Nature can do to manufacture green chemicals for human society.