New Strategies for Stereoselective Radical Biocatalysis

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Abstract: Despite the widespread applications of radical chemistry in both small molecule and macromolecule synthesis, it remains challenging to control the stereochemistry of radical transformations and to discover novel modes of radical catalysis which are not known in either organic chemistry or biochemistry. Combining synthetic chemistry, enzymology, and *de novo* protein design and protein engineering, our group has been actively advancing new biocatalytic strategies for stereoselective free radical processes. First, by capitalizing on the innate redox properties of first-row transition-metal cofactors, we repurposed and evolved diverse natural metalloproteins to catalyze unnatural radical reactions in a stereocontrolled fashion. Second, by merging redox catalysis and biocatalysis, we advanced a novel mode of pyridoxal radical biocatalysis which is new to both chemistry and biology. Cooperative photobiocatalysis allowed us to reprogram structurally and functionally diverse pyridoxal phosphate (PLP)-dependent enzymes as radical enzymes, leading to novel radical PLP enzymology. Pyridoxal radical biocatalysis provides stereoselective and protecting-group-free access to numerous useful non-canonical amino acids, including those bearing a stereochemical triad and/or tetrasubstituted stereocenters which remained difficult to prepare by other chemical and biological means. The ability to perform diversity-oriented synthesis combinatorially through previously elusive biocatalytic C–C bond formation marks a synthetically valuable advance, paving the way for broader adaptation and application of biocatalysis in medicinal chemistry. Furthermore, we demonstrate that the exploitation of biocatalyst-photocatalyst synergy affords a new paradigm to design and develop a range of stereoselective intermolecular radical reactions using new mechanisms.

Biosketch: Dr. Yang received his Ph.D. degree in Organic Chemistry in 2016 under the guidance of Prof. Steve Buchwald at MIT. As an NIH Postdoctoral Fellow working with Prof. Frances Arnold at Caltech, Dr. Yang studied biocatalysis and protein engineering. Dr. Yang started his independent career in 2020 in the Department of Chemistry and Biochemistry at the University of California Santa Barbara, where he was promoted to Associated Professor in the Departments of Chemistry and Biochemistry and Bioengineering in 2025. Using an interdisciplinary approach combining synthetic chemistry, synthetic biology, computational chemistry and computational biology, the Yang lab reprograms nature's biosynthetic machineries and designs *de novo* protein catalysts to access reaction space well beyond the native biochemical landscape. The Yang lab coined metalloredox radical biocatalysis (2021) and pyridoxal radical biocatalysis (2023) as general strategies to advance novel enzyme functions not previously known in nature, including those which are unknown in both chemistry and biology. Dr. Yang is a recipient of the Regent's Junior Faculty Fellowship Award (2021), Faculty Career Development Award (2022), National Science Foundation (NSF) CAREER Award (2022), National Institutes of Health (NIH) Maximizing Investigators' Research Award (2022), Thieme Chemistry Journals Award (2023), Army Research Office (ARO) Young Investigator Award (2023), Packard Fellowship (2023), Sloan Research Fellowship (2024), Department of Energy (DOE) Early Career Award (2024), Amgen Young Investigator Award (2024), Novartis Early Career Award (2025), Camille Dreyfus Teacher-Scholar Award (2025), and NAS Frontiers of Science Fellow (2026). Dr. Yang has been an Associate Editor of *Organic Letters* and a Howard Hughes Medical Institute (HHMI) Freeman Hrabowski Scholar since 2025.