ACCOUNTS of chemical research

Editorial

Cite This: *Acc. Chem. Res.* 2019, 52, 1145−1145

pubs.acs.org/accounts

New "Cats" in the House: Chemistry Meets Biology in Artificial Metalloenzymes and Repurposed Metalloenzymes

Guest Editorial for the Accounts of Chemical Research special issue on "Artificial Metalloenzymes and Abiological Catalysis of Metalloenzymes"

It is generally recognized that Wilson's and Whitesides' 1978 paper entitled "Conversion of a Protein to a Homogeneous Asymmetric Hydrogenation Catalyst by Site-Specific Modification with a Diphosphinerhodium(I) Moiety"[1] marked the birth of artificial metalloenzymes (ArMs). Such hybrid catalysts result from combining a non-natural cofactor with a protein scaffold. Thanks to the progress achieved in recombinant protein engineering, ArMs have witnessed a revival in the past 20 years. Accordingly, the challenges leading Wilson and Whitesides to conclude "The catalyst system...is not a practical asymmetric catalyst" are being overcome. This issue of *Accounts of Chemical Research* summarizes the progress achieved in the development of abiotic reactivity of natural metalloenzymes (repurposed enzymes, RepEns hereafter) and the construction of ArMs for an even broader range of abiotic processes.

Despite the significant improvements achieved upon subjecting an enzyme to multiple rounds of mutagenesis, the range of reactions catalyzed by enzymes is more limited than the range of reactions catalyzed by organometallic complexes or coordination complexes. To circumvent this restriction, and fascinated by the power of protein engineering and directed evolution, chemist's (re)considered the possibility of introducing abiotic cofactors within a protein around the turn of the millennium. Since then, the progress achieved in this field has led to a wide range of new-to-nature reactions catalyzed by RepEns and ArMs, suggesting that essentially any water-compatible organometallic catalyst may be endowed with a genetically encoded and evolvable protein scaffold. Reactions contained within this issue include Fischer−Tropsch reactions, cyclopropanations, C−H activation reactions, cross-couplings, olefin metatheses, (photo)catalytic CO_2 reduction, site-selective post-translational protein modifications, and gated multielectron transfers.

Capitalizing on a well-defined second coordination sphere provided by the protein around the metal cofactor, researchers have modified (artificial) metalloenzymes to react with exquisite levels of selectivity including enantio-, diastereo-, chemo-, and regioselectivity. Such catalyst control has been made possible by combining the tools of chemistry and biology. Half a century of organometallic catalysis offers a rich ground to select transition metal complexes that may bestow the host protein with initial (abiotic) catalytic activity. This activity then can be improved by genetic means. Identification of critical amino-acid residues to subject to mutagenesis may be guided by either computational information, an educated guess, or random mutagenesis throughout the entire protein. Noteworthy improvements summarized in this issue include rates, turnover numbers, redox potentials, and biocompatibility.

Thanks to nearly 20 years of experience, privileged protein scaffolds and robust anchoring strategies have been identified and made suitable for a broad range of catalytic applications. For example, hemoproteins bearing a non-native metal, cofactor, or decoy molecule have attracted significant interest, affording some of the best-in-class ArMs, with rates and turnover numbers rivaling natural enzymes. Cytochrome cb_{562} has been used to design novel protein interfaces and assemblies and has been shown to act as an *in vivo* artificial hydrolase. Building on Whitesides' lead, (strept)avidin has been shown to anchor nearly any biotinylated metal cofactor. Non-natural amino acids have been used to introduce a photosensitizer or to anchor abiotic cofactors within the multidrug resistance regulator LmR or the polyprolyl oligopeptidase POP. Finally, *de novo* artificial metalloenzyme design has led to three-stranded coiled-coils and four-helix bundles.

We hope that this set of Accounts describing these types of systems highlights the rapid progress and long-term potential of performing chemical synthesis with catalysts that combine concepts and structures of homogeneous catalysis with those of biocatalysis.

John F. Hartwig, Guest Editor
University of California, Berkeley
Thomas R. Ward, Guest Editor
University of Basel

AUTHOR INFORMATION

ORCID

John F. Hartwig: 0000-0002-4157-468X
Thomas R. Ward: 0000-0001-8602-5468

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

REFERENCES

(1) Wilson, M. E.; Whitesides, G. M. Conversion of a Protein to a Homogeneous Asymmetric Hydrogenation Catalyst by Site-Specific Modification with a Diphosphinerhodium(I) Moiety. *J. Am. Chem. Soc.* **1978**, *100*, 306−307.

Published: May 21, 2019

DOI: 10.1021/acs.accounts.9b00154
Acc. Chem. Res. 2019, 52, 1145−1145