JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Spotlights

Spotlights on Recent *JACS* Publications

Cite This: *J. Am. Chem. Soc.* 2022, 144, 1067−1068
Read Online
ACCESS | Metrics & More | Article Recommendations

BACTERIA BECOME TINY CATALYTIC SYNTHESIS VESSELS

Artificial metalloenzymes, made from protein scaffolds incorporating synthetic metal complexes, combine the versatility of transition-metal catalysts with the shape selectivity of enzymes. Until now, getting the metal complex into the cell has been difficult, and the reactivity of artificial enzymes in living cells has been limited. John Hartwig and colleagues use living cells of EcN, a non-pathogenic strain of *E. coli*, as reaction vessels to assemble artificial metalloenzymes that catalyze further chemical reactions (DOI: 10.1021/jacs.1c10975).

An iridium-containing porphyrin enters the bacterial cells from the growth medium via a chromosomally encoded outer-membrane transporter. The resulting enzyme catalyst drives site-selective, enantioselective carbene insertion into benzylic C−H bonds. The authors also identify a new transporter that is more efficient at taking iridium porphyrins into the cell cytoplasm than the heme transporter that they had originally assumed was the conduit.

Using EcN as a whole-cell screening platform eliminates the need for laborious processing procedures. This drastically increases the ease and throughput of screening artificial metalloenzymes to identify species with the best catalytic properties. This research presents a way to use biological systems to assemble similar catalysts, and it broadens the applications of artificial metalloproteins in catalyst-assisted organic reactions.

Nancy McGuire Ph.D.

MAKING E3 LIGASE RECRUITERS MORE UBIQUITOUS

E3 ligases are a class of enzymes that facilitate the ubiquitylation and degradation of various protein substrates. E3 ligases hold promising applications in the field of targeted protein degradation, in which disease-implicated proteins are specifically degraded. However, the E3 ligase and protein substrate must be physically co-localized to enable enzyme activity.

Now Daniel Nomura, Michael Rape, and co-workers report a proteolysis-targeting chimera (PROTAC), a heterobifunctional compound containing ligands for the E3 ligase FEM1B and a protein target that serve to recruit the enzyme to the substrate (DOI: 10.1021/jacs.1c03980). To identify a small-molecule ligand for FEM1B, the researchers screened 566 compounds and discovered that the chloroacetamide EN106 binds FEM1B through a covalent reaction with its Cys186 residue. Chemoproteomic analysis in cells demonstrated that the FEM1B-EN106 interaction maintained suitable proteome-wide efficiency and selectivity. The team then synthesized PROTACs consisting of EN106 linked to a compound that binds either the BRD4 or BCR-ABL protein. The team observed significantly reduced expression of BRD4 or BCR-ABL when cells were treated with the corresponding PROTAC. While the potency and pharmacokinetic properties of EN106 may be optimized, this work provides a framework for the development of E3 ligase-targeting PROTACs and underscores the value of expanding the suite of synthetic E3 ligase recruiters.

Sarah Anderson

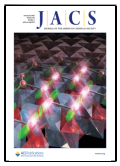
NOW YOU SEE ME—REFINING DETECTION METHODS FOR ULTRA-FAST PROTEINS

Proteins are dynamic and flexible molecules that fluctuate between different conformations to perform highly regulated functions crucial to sustaining life. These interconversions can span a wide range of time scales, anywhere from nanoseconds to milliseconds. Understanding protein dynamics is essential for a more complete picture of protein function and for further developing the relation between protein sequence, structure, and function. As one might imagine, characterizing quick conformational changes requires sophisticated technology that enables capturing rapidly occurring movements with high sensitivity.

At present, fluorescence-based strategies, including single-molecule Förster resonance energy transfer (smFRET) and nanosecond fluorescence correlation spectroscopy (nsFCS), have become indispensable technologies used to discern conformational dynamics of proteins. But, as with any technology, there are limitations. nsFCS, for instance, is useful for characterizing dynamics that occur within hundreds of nanoseconds. Rearrangements that occur beyond the limit of detection would not be recognized. Thus, a dimension of conformational dynamics remains poorly characterized, as current approaches are not inclusive of a full range of time scales.

To overcome this limitation, Benjamin Schuler and co-workers have contributed to the growing toolkit of increasingly sophisticated methods for studying protein dynamics (DOI:

Published: January 26, 2022



https://doi.org/10.1021/jacs.2c00603
J. Am. Chem. Soc. 2022, 144, 1067−1068

10.1021/jacs.1c09387). The authors describe a modified nsFCS approach using nanophotonics to extend the accessible timescales down to about 5 ns. At present, little is known about what proteins do on nanoseconds time scales—this is where the approach truly shines. The technique can facilitate a more holistic understanding of biomolecular dynamics in this regime, as the authors demonstrate with complimentary molecular dynamics simulations. Moreover, the technique offers higher throughput and has significantly lower acquisition times.

Kelly Montgomery

TUNING MONOMER STRUCTURE TO IMPROVE THERMODYNAMICS FOR CHEMICALLY RECYCLABLE POLYMERS

Chemical recycling of polymers to their constituent monomer entities (CRM) is an attractive approach to address the sustainability of this ubiquitous and useful class of materials. The key to an effective, efficient, and stable CRM process lies in its thermodynamics: the depolymerization conditions need to be practical, and the polymer needs to remain stable. Now Junfeng Zhou, Devavrat Sathe, and Junpeng Wang have examined the thermodynamics of a series of fused ring cyclooctenes to establish design principles for developing monomers for CRM polymers (DOI: 10.1021/jacs.1c11197).

Systems based on cyclic monomers generally have favorable thermodynamics through ring-opening polymerization and ring-closing depolymerization processes. Polymer chemists explore the enthalpy and entropy changes of polymerization of cyclooctene monomers with an additional ring fused at the 5,6 positions. They find that enthalpic and entropic factors can be tuned independently, both through the size of the fused rings and through the substituents. Additionally, geminal substituents that are not directly attached to the cyclooctene still have a significant effect on the polymerization thermodynamics and can promote depolymerization. These findings point to strategies to tune the polymers' thermomechanical properties and promote depolymerization for a more effective and efficient CRM process.

Dalia Yablon Ph.D.

https://doi.org/10.1021/jacs.2c00603
J. Am. Chem. Soc. 2022, 144, 1067−1068