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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Spotlights on Recent *JACS* Publications

CLICK CHEMISTRY DRIVES IN VIVO GLYCOMICS

Protein glycosylation is a regulated process, varying between tissues and during disease. Researchers naturally wish to study these differences, and existing methods primarily study glycoproteins biochemically. Until recently, researchers have had no way to label and visualize glycoproteins in intact tissues in vivo. Now Xing Chen and colleagues describe a click chemistry-based "metabolic glycan labeling" approach to do just that in rodents (DOI: 10.1021/ja508484c).

The team delivers *N*-azidoacetylmannosamine (Ac_4ManNAz), a glycan precursor, to rats via intraperitoneal injection. Seven days later, sialylated glycoproteins can be visualized microscopically in intact heart tissue using aza-dibenzocyclooctyne-Fluor 488, a fluorescent click chemistry reagent. Alternatively, glycoproteins can be isolated, and subsequently identified by mass spectrometry, using alkyne-biotin.

Applying these methods to a rat model of cardiac hypertrophy, Chen's team has observed a sharp increase in surface protein glycosylation in disease, identifying several hundred different sialylated proteins, a "significant number" of which have been modified differentially in normal and diseased tissue.

The findings potentially implicate protein sialylation in cardiac development and pathogenesis, the authors write. But, they add, the method is also generalizable to other tissues, and to other sugars.

Jeffrey M. Perkel

GOING BIG WITH SOLID-STATE NMR SPECTROSCOPY

Interactions between proteins govern many biological processes. Protein−antibody complexes are of particular interest due, in part, to the increasing development of antibodies as therapeutics. Progress is hindered, though, because protein−antibody complexes can be quite large, making it difficult to study their structures using standard approaches. For example, line broadening in solution-state nuclear magnetic resonance (NMR) spectroscopy increases with molecular size. However, line widths in solid-state NMR are size-independent, offering a promising approach for the study of large protein complexes.

Solid-state NMR comes with its own drawbacks, such as line broadening due to variation in local magnetic fields. To overcome some of these challenges, a team led by Stephan Grzesiek, Ago Samoson, and Józef Lewandowski has developed a solid-state NMR approach using magic-angle spinning, optimizing spinning frequency to minimize line broadening (DOI: 10.1021/ja5069992). As a test case, the researchers characterize a protein G domain bound to full-length immunoglobulin G, prepared through simple precipitation. In minutes to hours, they obtain well-resolved spectra with adequate signal-to-noise using an order of magnitude less protein than is typical in NMR experiments of protein complexes. Comparing the complex's spectra to those of the constituent proteins free in solution has allowed the researchers to map out the residues involved in the protein−protein interactions.

Erika Gebel Berg, Ph.D.

CHEAP CATALYST SYSTEM SELECTIVELY REDUCES CARBON DIOXIDE

One possible approach to handling excess carbon dioxide in the atmosphere is to find ways to convert the gas into useful compounds. Chemists look to convert carbon dioxide into commodity chemicals. The first step in many of these processes is to reduce the carbon dioxide to compounds like carbon monoxide, formaldehyde, or methanol. Unfortunately, many catalysts used for these reductions are based on expensive metals like rhenium or ruthenium. The reactions also struggle with selectivity, tending to produce hydrogen gas as a byproduct.

Julien Bonin, Marc Robert, and Mathilde Routier have developed an iron-based catalyst to reduce carbon dioxide to carbon monoxide (DOI: 10.1021/ja510290t). They include 9-cyanoanthracene as a photosensitizer to stabilize the iron catalyst and to drive the reaction toward making carbon monoxide. Little to no hydrogen is formed after the system is irradiated for more than 50 h with visible light.

This catalyst system is noteworthy because of its stability, selectivity, and inexpensive components.

Melissae Fellet, Ph.D.

PYRITE SOLAR CELLS' TROUBLES LIE DEEPER THAN THE SURFACE

Researchers have been studying iron pyrite (fool's gold, FeS_2) as a promising semiconductor for solar energy conversion since the 1980s. Its abundance and good theoretical properties suggest potential for large-scale inexpensive and sustainable solar cell technologies, and much research has focused on the synthesis of pyrite materials. Yet despite extensive efforts and a few promising early reports, pyrite's solar conversion efficiency and, specifically, its photovoltage remain very low.

Song Jin, Miguel Cabán-Acevedo, and colleagues investigate the cause of this puzzle by studying crystal pyrite's electrical transport properties, optical behavior, surface properties, electrochemical behaviors, and more (DOI: 10.1021/ja509142w). Through this research, the authors completely characterize pyrite's bulk and surface defect states and construct a detailed energy band diagram.

Pyrite's low photovoltage had previously been attributed to defects at the semiconductor surface, but the researchers find that a deeper problem arises from defect states, likely due to sulfur vacancies, throughout the pyrite crystal. These deep defects cause the near-surface region of the material to behave like a degeneratively doped semiconductor and reduce the photovoltage. Because the problem arises from intrinsic bulk defects, surface treatments may not be sufficient to improve the material's solar conversion efficiency, the authors say. To improve photovoltage in pyrite, researchers will have to find viable means to eliminate sulfur vacancies, or add beneficial dopants.

Jenny Morber, Ph.D.

Published: December 3, 2014

dx.doi.org/10.1021/ja512261r | *J. Am. Chem. Soc.* 2014, 136, 17357−17358

SYNERGISTIC MUTATIONS REVERSE ENANTIOSELECTIVITY OF AN ENZYMATIC CATALYST

Phenyl acetone monooxygenase (PAMO) is a thermally stable enzyme that can catalyze asymmetric sulfoxidation of thioethers to chiral sulfoxides, an important class of drug precursors. However, wildtype PAMO is generally inefficient in performing such oxidations with high enantioselectivity.

This challenge has prompted Manfred T. Reetz and colleagues to modify PAMO into variants with both (*R*)- and (*S*)-selectivity via directed evolution, a natural selection-mimicking technique that is used to accurately modify proteins on the molecular level by selectively mutating the encoding genes (DOI: 10.1021/ja5098034).

Deconvolution studies unexpectedly reveal that, while the best mutant, a quadruply mutated species, is highly (*R*)-selective, its four respective mutants with only a single mutation each are all (*S*)-selective. In addition, these studies also illustrate how these mutations interact cooperatively during the evolution process, leading to inversion of enantioselectivity rather than the potentially expected simple additive reinforcement, which is further corroborated by computational docking analysis.

The researchers not only successfully reverse, by directed evolution of PAMO, the enantioselective preference of the enzyme toward the sulfoxidation of thiols, but also present the most extreme example of synergism in protein engineering. This study certainly contributes to the better understanding of synergistic mutational effects, again affirming the notion that although genetic mutations in proteins follow nonlinear pathways, it is always possible to develop tools in directed evolution to overcome this unpredictable enzymatic behavior.

Xin Su, Ph.D.

EFFICIENT HEPATIC GENE KNOCKDOWN WITH SMALL INTERFERING RNA

Since its discovery in 1998, RNA interference has held tantalizing clinical potential. In RNAi, small interfering RNAs (siRNAs) target complementary mRNAs for degradation. By targeting mutant transcripts in affected tissues, researchers should be able to ease disease symptoms by inhibiting synthesis of disease-causing proteins.

Typically, siRNAs are formulated with lipoparticles, nanoparticles, or other vehicles, but these designs generally must be delivered intravenously. Now Muthiah Manoharan and Kallanthottathil Rajeev, of Alnylam Pharmaceuticals, and their collaborators report that siRNA conjugation to *N*-acetylgalactosamine (GalNAc) is sufficient to efficiently knock down target gene expression in the mouse liver following subcutaneous delivery (DOI: 10.1021/ja505986a).

The research team synthesizes bi- and triantennary GalNAc building blocks that they can couple to siRNAs during their synthesis. Triantennary designs are taken up by primary mouse hepatocytes both in culture and in the liver following subcutaneous administration, where they knock down mRNA abundance, in one case yielding efficient mRNA knockdown at 1 mg/kg, an effect that could be extended for months with daily dosing.

"The optimally chemically modified siRNA–GalNAc conjugates are hepatotrophic and long-acting and have the potential to treat a wide range of diseases involving liver-expressed genes," the authors write.

Jeffrey M. Perkel