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

Spotlights on Recent *JACS* Publications

CHEMICALLY STITCHING DESIGNER PROTEIN DRUGS

Protein drugs are proving to be powerful tools in fighting diseases from cancer to diabetes, and glycoproteins—defined by a carbohydrate group critical for bioactivity attached to the peptide structure—comprise the largest group among these tools. But product variability and purification steps needed to remove viruses, bacteria, and other genetic material handicap the utility of cell systems that produce such protein drugs.

Using the cytokine interferon-β (IFN-β) as a model glycoprotein, Yasuhiro Kajihara and colleagues developed a chemical synthesis process for purified homogeneous glycoprotein drugs (DOI: 10.1021/ja2109079). Synthesizing the glycopeptide using a flexible technique—Fmoc solid-phase protein synthesis—that allows inclusion of unnatural amino acids and structural modifications, the researchers prepared the human IFN-β in segments, stitched them together using a chemical ligation technique, and folded the protein using dialysis under redox conditions. This synthesized, homogeneous IFN-β glycoprotein exhibited very potent *in vivo* antitumor activity and is an optimized form of the expressed IFN-β, whose carbohydrate is only about 80−95% homogeneous due to cell system product variability.

The chemical approach to synthesizing purified homogeneous protein drugs offers a look at the relationship between carbohydrate structure and glycoprotein bioactivity and provides a powerful method to create designer glycoproteins to treat disease. **Kenneth J. Moore**

DNA ORIGAMI RULER REVEALS DISTANCE-DEPENDENCE OF ENZYME PAIR ACTIVITY

Researchers have taken advantage of DNA self-assembly to generate nanostructures for studying how multi-enzyme complexes channel molecules between one another. The nanostructures, known as DNA origami, are composed of a long strand of DNA that is "stapled" together with many short DNA strands. The predictability of DNA base-pairing allows researchers to design the DNA strands to yield nanostructures with well-defined properties.

Hao Yan and co-workers engineered DNA nanostructures to position two enzymes, known as glucose oxidase (GOx) and horseradish peroxidase (HRP), on nano-sized DNA origami tiles (DOI: 10.1021/ja300897h). After tagging the enzymes with DNA, the research team immobilized the enzymes at nanometer-length distances apart and studied the effect of separation distance on the activity of the enzyme pair.

Prior to the introduction of DNA origami to the chemistry toolkit in 2006, few methods existed for spatially controlling the position of multiple enzymes in noncellular environments at the nanometer level. The results from this study shed light on the process of inter-enzyme substrate diffusion, which is a crucial component of efficient enzyme activities *in vivo*. **Christine Herman**

HEAVYWEIGHTS BOND IN THE RING

The Diels−Alder reaction—a cycloaddition reaction capable of efficiently producing both simple and complex ring structures—is a stalwart of introductory organic chemistry course syllabi. The reaction is useful for synthesizing natural products, polymers, and other materials. Most commonly all-carbon systems participate in cycloaddition reactions, but heavier elements such as transition metals can also participate in the cyclizations. Group 14 dimetallenes have been studied in cycloaddition reactions, but not much is known about heavier group 13 alkene analogues.

Philip Power and co-workers performed cycloaddition reactions between digallene, a heavier group 13 alkene analogue, and various polyolefins (DOI: 10.1021/ja301247h). They found that digallene is more reactive than its alkene counterpart, allowing it to undergo cyclization reactions in ambient conditions. Digallene is readily incorporated into higher-order rings, while catalytic conditions would be required for similar all-carbon systems. Furthermore, cyclization reactions involving heavier group 13 dimetallenes can be easily reversible.

Heavier group 13 dimetallenes were shown to be particularly useful for higher-order cycloaddition reactions, which are more challenging with all-carbon systems and heavier group 14 dimetallenes. Moreover, understanding the properties of heavier group 13 alkene analogues in cycloaddition reactions could enable the synthesis of new nanomaterials, polymers, and other compounds with ring architectures. **Yun Xie, Ph.D.**

Published: March 27, 2012

dx.doi.org/10.1021/ja302665h | *J. Am. Chem. Soc.* 2012, 134, 5717−5717