

Spotlights on Recent JACS Publications

■ BIOPHARMACEUTICALS: POLYMERS PROVIDE VARYING DEGREES OF ANTIBODY SHIELDING

Virus-like particles (VLPs) are excellent candidates for bio-based nanotherapeutics, owing to their monodispersity, well-defined shapes and sizes, and ability to be tailored for the precise placement of chemical tags to conjugate drugs, polymers, and targeting ligands. But there are numerous challenges to developing a successful biopharmaceutical. Chief among them is ensuring that the drug does not evoke an immune response from the patient. One approach to immune evasion involves tagging bio-based drugs with polymers, such as methoxypoly-(ethylene glycol) (mPEG), which has been found to increase a drug's circulation half-life while decreasing antigenicity.

Jonathan Pokorski and his team compare mPEG with two other water-soluble polymers—polyacrylate and polynorbornene—when conjugated to icosahedral VLPs, and find vastly different polymer conformations and antibody-shielding potential (DOI: [10.1021/jacs.6b11643](https://doi.org/10.1021/jacs.6b11643)). The researchers create the VLP-polymer conjugates and use small-angle neutron scattering and cryo-electron microscopy to investigate the structure and conformation of the polymers on the surface. Among the three polymers tested, polynorbornene offers the greatest antibody shielding while having the smallest hydrodynamic volume. The results may help lay the groundwork for the future development of next-generation biopharmaceuticals based on VLPs.

Christine Herman, Ph.D.

■ IMPROVING TOOLS FOR DYNAMICS SIMULATIONS

Simulation capabilities that complement and enhance our understanding of chemical reaction dynamics are continually improving through development of both new methods and faster computation times. Various tools have different ways of representing a potential energy surface (PES), calculating trajectories, and setting initial conditions for subsequent calculations. In this Perspective, William Hase and co-authors describe direct chemical dynamics simulations, the technologies that take advantage of chemical dynamics and electronic structure theory (DOI: [10.1021/jacs.6b12017](https://doi.org/10.1021/jacs.6b12017)).

The method has been applied to study classic reactions such as bimolecular S_N2 nucleophilic substitutions and unimolecular decomposition. One of its major advantages is that, instead of describing the PES as a potentially crude analytical function, in this method the PES is calculated “on the fly” from electronic structure theory.

Direct dynamics simulations are widely used, from assisting in the interpretation of experimental results to gaining a deeper understanding of when statistical theories are valid for predicting reaction mechanisms. Simulations can also push new frontiers with the discovery of new reaction pathways and dynamics. Improving the calculation efficiency to reduce computation times is important for this method's expanding role so that it can be successfully applied to larger molecular systems.

Dalia Yablon, Ph.D.

■ EVALUATING ERROR IN NMR CRYSTALLOGRAPHY

The first thing most scientists want to know about a crystal structure is how reliable it is, which is summed up in one nifty little number, the root-mean-square deviation (RMSD) of atomic positions. The precise location of atoms is particularly important in the pharmaceutical industry, where the determination of chemical structure is a central tool in drug development. In recent years, NMR crystallography has emerged as an alternate approach to solving 3-D structures of molecules, with the advantage of using powders instead of single crystals, but NMR crystal structures did not come with the same type of error estimate. Lyndon Emsley and Albert Hofstetter have developed a method for assessing the equivalent of a RMSD for structures determined by NMR crystallography, allowing scientists for the first time to ascertain their reliability (DOI: [10.1021/jacs.6b12705](https://doi.org/10.1021/jacs.6b12705)).

The researchers' approach is based on molecular dynamics simulations and density functional theory calculations combined with experimentally and computationally determined NMR chemical shift uncertainties. They test the method on cocaine, flutamide, flufenamic acid, the potassium salt of penicillin G, and the drug 4-[4-(2-adamantylcarbonyl)-5-*tert*-butylpyrazol-1-yl]-benzoic acid (AZD8329). For cocaine, the determined uncertainty corresponds to an RMSD of 0.17 Å, providing a 2-fold greater positional accuracy than that obtained using single-crystal X-ray crystallography.

Erika Gebel Berg, Ph.D.

■ ENZYME ASSAY SOLVES STEREOCHEMISTRY IN ANTIBIOTIC BIOSYNTHESIS STEP

David Cane and colleagues present a new chemoenzymatic assay that can determine the stereochemistry of an important class of intermediates produced during the biosynthesis of polyether antibiotics (DOI: [10.1021/jacs.7b00278](https://doi.org/10.1021/jacs.7b00278)).

Polyether ionophores such as the antibiotics nanchangmycin and salinomycin are used in poultry management to promote animal growth and treat parasitic infections. Though researchers have determined the general mechanism of their biosynthesis, many details remain to be clarified. This biosynthesis is orchestrated by a modular polyketide synthase that first generates a parent branched-chain, unsaturated polyketide carboxylic acid. In one step of the biosynthesis, a ketoreductase domain in the modular enzyme is thought to generate C2-epimerized 2-methyl-3-ketoacyl-acyl carrier protein (ACP) intermediates.

Cane's group has developed a coupled ketosynthase-ketoreductase assay to determine the 2-methyl configuration of any of these 2-methyl-3-ketoacyl-ACP intermediates. They confirm that a ketosynthase domain of nanchangmycin synthase generates exclusively (2*R*)-2-methyl-3-ketopentanoyl-ACP, which then undergoes inversion of configuration at the 2-methyl group, catalyzed by a paired, redox-inactive ketoreductase domain.

Deirdre Lockwood, Ph.D.

Published: March 8, 2017