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

Spotlights on Recent *JACS* Publications

NMR STRUCTURE REVEALS SECRETS OF FLU VIRUS RESISTANCE

Though their genomes are small, viruses are clever, rapidly evolving to outsmart modern medicine. This arms race is evident in the influenza A M2 protein, a transmembrane protein essential for viral replication. In low pH conditions, the M2 protein forms a tetramer that conducts protons, facilitating the unpacking of the viral genome into the cytosol of the infected cell. A single mutation in the M2 protein—a serine-to-asparagine swap at position 31 (S31N)—makes the virus resistant to anti-influenza drugs.

Using magic angle spinning NMR spectroscopy, Robert Griffin and colleagues have solved the structure of the mutant M2, gaining new insight into the mechanism of resistance (DOI: 10.1021/jacs.5b04802). The NMR samples include lipid bilayers, which mimic cellular membranes and create a biologically relevant environment. Using a series of innovative dipole recoupling experiments, the researchers solve a high-resolution structure of tetrameric mutant M2, a dimer of dimers, in the lipid bilayers. The structure helps to explain the mechanism of proton conduction. Additionally, the side chain of the mutated residues blocks the sites where anti-influenza drugs bind, explaining drug resistance and offering an opportunity to develop new medications that overcome resistance.

Erika Gebel Berg, Ph.D.

DETECTING THE MIDDLE MAN IN ALZHEIMER'S DISEASE

Sihyun Ham, Thomas Wisniewski, Young-Tae Chang, and co-workers report the identification of a molecular probe for oligomeric amyloid β-peptide (Aβ), a substance implicated as the causative agent of Alzheimer's disease (DOI: 10.1021/jacs.5b06190). Investigating the mechanism of the neurotoxicity that characterizes Alzheimer's disease and plagues over 35 million individuals across the globe has been notoriously challenging, in part due to the heterogeneity of Aβ, which includes monomeric, oligomeric, and fully aggregated species, as well as the dearth of effective tools to explore the disease at the molecular level.

To identify a molecule capable of differentiating oligomeric Aβ over monomeric and aggregated Aβ, the authors use a high-throughput and high-content screening approach. They assess the ability of 3500 fluorescent compounds to selectively bind Aβ oligomers in live cells. This screening effort has identified a compound termed BoDipy-Oligo, or BD-Oligo, that monitors Aβ oligomer formation in vitro. Moreover, BD-Oligo can permeate the blood–brain barrier, facilitating visualization of oligomeric Aβ in mouse models of Alzheimer's disease. In addition to providing a new mechanistic tool for the study of Alzheimer's disease, BD-Oligo offers an exciting jumping-off point for the development of new diagnostic and therapeutic agents for this devastating disease.

Eva J. Gordon, Ph.D.

A BETTER DETOUR TO AROMATIC AMINATION

Aromatic amines—fundamental building blocks often seen in natural products, pharmaceuticals, and organic materials—are usually prepared by C–H amination. Electrochemical oxidation is among the more promising solutions for synthesis of these molecules, especially for direct coupling involving functionalized primary alkylamines. But this method still suffers from challenges such as low substrate compatibility and over-oxidation.

Now, Jun-ichi Yoshida and his team circumvent these hurdles by taking a slight detour, in which they convert alkylamines into heterocycles prior to the electrooxidative coupling with aryl partners (DOI: 10.1021/jacs.5b06526). Unlike the protecting group strategy, heterocyclization with nitriles shields amines from oxidation without decreasing their nucleophilicity, and the amine products are easily regenerated by nitrile removal after electrolysis.

The researchers have demonstrated excellent chemoselectivity, broad substrate scope, and high compatibility with functional groups for the new cyclization–electrochemical amination reaction. They also significantly improve the synthesis of a mutagenic compound by providing direct access to the intermediate aryl amine. This metal-free alternative is a cleaner and more efficient strategy for the synthesis of *N*-alkylanilines with oxygen- and nitrogen-bearing alkyl groups.

Xin Su, Ph.D.

NEW STRATEGY EATS UP ALZHEIMER'S PROTEIN PLAQUES

One of the hallmarks of Alzheimer's disease is the accumulation of cytotoxic amyloid β-protein (Aβ) tangles. Proteinase digestion of these tangles represents a potential therapeutic strategy, but Aβ oligomers are relatively resistant to such enzymes. Now Bing Xu and colleagues demonstrate a method for dissociating the protein tangles, rendering them susceptible to proteinase treatment (DOI: 10.1021/jacs.5b05888).

Exploiting the observation that normal prion proteins are more heavily glycosylated than pathogenic prion proteins, the researchers devise a strategy they call "supramolecular glycosylation-assisted proteolysis", which non-covalently introduces sugar groups into pre-existing tangles. Xu and colleagues create two short peptides to model Aβ oligomers. The peptide P-**1** is susceptible to proteinase K as a monomer but resistant when assembled into a hydrogel. Its interacting partner GP-**2**, a tetrapeptide flanked by thymine and glucosamine, is protease-resistant. In the presence of GP-**2**, the team finds, the P-**1** hydrogel dissolves, restoring proteinase sensitivity to the monomer.

"This novel and facile approach contributes a useful insight that may assist molecular design for degrading cytotoxic oligomers of peptides or aberrant proteins that are plausible causal agents of neurodegenerative diseases," the authors conclude.

Jeffrey M. Perkel

Published: August 11, 2015

DOI: 10.1021/jacs.5b08475
J. Am. Chem. Soc. 2015, 137, 10017–10017