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Spotlights on Recent *JACS* Publications

GELLING WITH ANTI-INFLAMMATORY GELS

Nonsteroidal anti-inflammatory drugs, or NSAIDs, are used extensively for pain relief, with an estimated 30 billion doses consumed annually in the United States alone. However, NSAIDs are associated with relatively common and sometimes dangerous gastrointestinal, renal, and cardiovascular side effects. The development of NSAIDS as topical agents is an attractive approach for circumventing some of these adverse events, since topical agents are applied directly to the site of injury which can minimize their exposure to the rest of the body.

Toward the development of NSAID-based topical agents, Bing Xu and co-workers report the generation of anti-inflammatory hydrogelators, small molecules that self-assemble into supramolecular nanomaterials in water (DOI: 10.1021/ja310019x). Using the crystal structure of cyclooxygenase-2—the enzyme target of many NSAIDs—to guide the design, the NSAID naproxen was converted to a hydrogelator by strategically attaching a few amino acids to the drug. Key to the success of this design was the use of D-amino acids, which improved the stability of the compounds and unexpectedly enhanced their potency. This promising approach for designing hydrogelators as topical drugs could be applied to other drugs suitable for topical administration as well. **Eva J. Gordon, Ph.D.**

COMPUTATIONAL MODELING YIELDS POSSIBLE CELIAC THERAPEUTIC

Celiac disease is an autoimmune reaction to proline- and glutamine-rich (PQ-rich) peptides from the gluten protein, α-gliadin. One therapeutic strategy is to provide celiac patients with an "oral enzyme therapeutic" (OET) that can digest those peptides, and several examples are in development. Now Justin Siegel and colleagues use computational modeling to design an efficient alternative that can function in the acidic environment of the stomach, resist digestive enzymes, and be expressed at high levels in soluble form (DOI: 10.1021/ja3094795).

The team built its OET on the scaffold of an acid-stable proteinase called kumamolisin-As from *Alicyclobacillus sendaiensis*. Using computational modeling of the protein structure, they identified mutations that could potentially tweak its substrate specificity toward PQ-rich peptides. The team tested 261 variants with up to seven mutations. One, dubbed "KumaMax", was 120 times more active than the wild-type enzyme on a synthetic PQ-substrate, functioned efficiently at pH 4, and was resistant to degradation by digestive proteinases. When tested with an immunogenic α-gliadin peptide, KumaMax degraded 95% within 50 min, whereas a natural stomach endopeptidase was inactive.

"Future work focused on the further characterization of this designed enzyme will ultimately shed light on its suitability for use as a therapeutic," the authors write. **Jeffrey M. Perkel**

SHORT IS STABLE IN ORGANIC RADICAL CATIONS

Stable organic radicals can be useful for building paramagnetic materials, such as conductive molecular electronic devices. However, radical cations are particularly susceptible to oxidation by O_2 in air. Making these compounds more stable to the atmosphere is a major challenge in radical chemistry. Radicals composed of 4,4′-bipyridinium ($BIPY^{\bullet+}$) units can be stabilized by encapsulating them in a "molecular flask". J. Fraser Stoddart and co-workers achieve this aim by incorporating the radicals into a [2]rotaxane, a molecule that has a ring unit assembled around a dumbbell unit (DOI: 10.1021/ja310060n).

The researchers made this series of sterically constrained rotaxanes from a cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) ring around a $BIPY^{2+}$ that had been incorporated into oligomethylene chains of varying lengths. The CBPQT unit can move back and forth across the chain, with the $BIPY^{2+}$ acting as a "molecular speed bump". Both experimentally and computationally, the researchers found that the shorter the $BIPY^{2+}$ dumbbell, the more stable these organic radicals were to atmospheric O_2. They speculate that the radical electron is delocalized across two or more $BIPY^{2+}$ units in the shorter rotaxanes. This method is a new way to create persistent organic radicals and may lead to the development of nanoelectromechanical technologies and paramagnetic materials. **Leigh Krietsch Boerner, Ph.D.**

NOVEL FLUORESCENT PROBE LIGHTS UP HUMAN CANCER CELLS

A new probe selectively lights up inside cancer cells and holds promise for applications in cellular imaging and surgical chemotherapeutic treatments.

Researchers led by Robin L. McCarley report the development of the small-molecule probe, made of a naphthalimide dye reporter coupled to a quinine quencher, which lights up only when it is selectively cleaved by an intracellular cancer-associated reductase enzyme, NQO1 (DOI: 10.1021/ja309346f). The probe can differentiate between NQO1-expressing and non-expressing cells and can be detected with flow cytometry, fluorescence imaging, two-photon microscopy, or the unaided eye. The team finds the probe has no significant effect on cell viability and is stable in vitro, revealing its potential for use in long-term cell-based studies.

Since the probe can be detected within cells using multi-photon fluorescence microscopy, it holds promise for applications in thick-specimen imaging, such as for the evaluation of pharmaceutical targets in vivo or ex vivo. Finally, because the probe can be seen by the unaided eye, it is a promising candidate for medical applications such as the surgical resection of cancerous tissues. This is the first demonstration of a small-molecule turn-on probe that targets an endogenous, intracellular cancer-associated enzyme. **Christine Herman, Ph.D.**

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