JACS
EDITORIAL

Published on Web 11/10/2010

# Supramolecular and Chemical Cascade Approaches to Molecular Sensing

Basic science knowledge continues to result in real-world applications in innovative ways. The field of molecular sensing is a prime example of how combining knowledge of chemical reactivity, supramolecular interactions, and photophysics yields practical tools in molecular biology, synthetic methodology, analytical chemistry, and other disciplines. The *Journal of the American Chemical Society* showcases an astounding diversity of imaginative and innovative approaches to molecular sensing. One goal of this *JACS* Select issue is to compile some examples from the past few years of supramolecular sensors, and what can be referred to as chemical cascade approaches, and highlight their utility. But most importantly, the over-arching goal is to inspire others to draw on their own basic science knowledge for the creation of new, novel, and practical molecular sensors.

Synthetic receptors designed to exploit supramolecular interactions have been used for decades in sensing applications. Most examples are based upon a receptor−spacer−reporter (RSR) paradigm, which has proven to be of great utility for optical probes, such as the Ca(II)-responsive indicators FURA-2 and INDO-1. Such probes have had a major impact on the chemical biology community and are still in very high demand. *JACS* is a showcase for new and novel examples. For instance, **Yoon** recently created a synthetic receptor that gave selective responses to ATP over AMP, ADP, CTP, TTP, and GTP.[1] The receptor contained four alkyl imidazolium groups for ion-pairing and two pyrenes for modulation of eximer emission. ATP levels could be qualitatively differentiated in HeLa cells. Using another fully designed synthetic receptor, **Fabbrizzi** demonstrated how selectivity for guanosine monophosphate over other monophosphates can be achieved by judicial placement of Cu(II) ions in a cryptate.[2] He used an indicator-displacement assay (IDA), rather than a RSR, to signal guest binding. Rather than specifically designing all aspects of a RSR or an IDA, **Y.-T. Chang** introduced a combinatorial approach,[3] creating 160 Knoevenagel-derived BODIPY conjugates from common aldehydes. Screening of this library revealed a cellular imaging probe for glucagon. Two years ago, **Lippard** took the RSR paradigm for imaging agents a step further by adding a fourth component for organelle-selective delivery.[4] A reactive moiety that targets the protein $O^6$-alkylguanine transferase (AGT) was added to a zinc-responsive probe. Organelle-specific fusion proteins with AGT directed the Zn(II) probe to specific cites in cells. Very recently, **C. Chang** appended a sulfur podand to a BODIPY reporter to monitor Cu(I), even in the presence of Cu(II), for the ratiometric imaging in live cells of ascorbate-induced increases in Cu(I) labile pools.[5] In an innovative supramolecular assembly approach, **Matile** designed synthetic membrane pores whose activity is switched on and off without and with inositol phosphates (IPs), respectively.[6] A fluorescence measure of membrane activity monitors the IP concentrations. Moving away from synthetic receptors, **He** targeted Cu(I) with a genetically encoded fluorescence resonance energy transfer sensor, wherein a metal-induced conformational change arising from ligation to an oligo-cysteine made a sensitive imaging agent.[7] Last, it should be noted that animal imaging is an important frontier for synthetic receptors/indicators. **Nagano** is paving the way with the recent creation of a bis-dye conjugate referred to as FOSCY-1 for monitoring reactive oxygen species, both in cells and in mouse models.[8] These few examples using synthetic receptors/reporters, combinatorial chemistry, and microscopy are contributing to a rebirth of the classic field of host/guest chemistry in a new practical arena: imaging agents.

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Triggering cascades of covalent bond-modifying reactions by the addition of specific analytes is an alternative to creating assays that rely on supramolecular interactions. Often, well-known reactions, when carried out within the context of novel reactants, will create or modulate the structures of chromophores or fluorophores upon addition of specific analytes. For example, **Sessler** used the classic benzil reaction to selectively decolorize a chromophore upon addition of the cyanide anion over other anions.[9] Further, completely new reactions are also attractive for reaction cascades. One quite innovative example for making cellular imaging agents is found in the work of **Hamachi**, where the binding of pyro- and triphosphates to a bis-zinc receptor leads to an elimination reaction that creates a fluorophore.[10] This reaction cascade allowed for ATP monitoring in vitro. Our own group (**Anslyn**) recently introduced a multistep reaction cascade that creates an imaging agent in vitro, initiated by a reaction with $NO^+$, which was used to indirectly image NO radicals in two different cell lines.[11] Many reaction cascades are built upon the knowledge of classic organic reaction mechanisms, and hence their exploitation in sensing represents fertile ground for physical organic chemists.

Proteomics is a field ripe for picking biological targets of interest for creating sensors. Enzymes are common targets, including proteases, phosphatases, transferases, and kinases. For example, **Kikuchi** took advantage of the long-lived luminescence of terbium complexes to create turn-on sensors for the presence of various proteases.[12] Using organic synthesis, peptide chains specific for calpains or leucine aminopeptidase, respectively, were appended to an antenna at the cleavage sites of these proteases. Protease activity liberates the antenna, which then transfers its excitation energy to Tb(III), resulting in a long-lived response to the proteases. **Imperiali** targeted kinase activity with a strategy that employs a metal-binding fluorophore covalently appended adjacent to the site of phosphorylation, which upon kinase activity binds exogenous magnesium, leading to chelation-enhanced fluorescence.[13] Combining facets of both of the previous examples with her own ingenuity, **Russell** created a family of reagents whose protonation modulates their color specifically in the presence of the breast cancer marker arylamine *N*-acetyltransferase.[14] In addition, **Zondlo** described a genetically encodable protein sequence that binds Tb(III) and turns on luminescence upon tyrosine phosphorylation events.[15] Last, **Schepartz** created a probe that specifically targets tetraserine motifs within peptides and engineered peptides and then used the probe for cell surface labeling.[16] Such coupling of chemical reactivity to supramolecular binding events, which in turn modulate an optical response, is an inspiration for other novel approaches to chemical sensing.

Besides proteomics and cellular imaging, another area that is benefiting from supramolecular receptors and reaction cascades is organic synthesis methodology development. **Jäschke** reported specialized fluorescent substrates for RNA-catalyzed Diels−Alder reactions whose fluorescence turned on upon cycloaddition, with the ultimate goal of using such designs in the screening of Diels−Alder catalysts.[17] As a further example of how sensors can be used in screening, **Wolf**[18] showcased optical approaches for the high-throughput screening of enantiomeric excess (ee) in analysis of parallel reactions. We both have created assays that report ee via UV/vis and CD spectral modulations that result from the binding of chiral guests to various synthetic receptors. In another endeavor to assist synthesis procedures, **Koide** used a reaction cascade that creates a fluorophore triggered by low levels of Pd(II) to monitor contamination by this metal in products created in various cross-coupling reactions.[19]

Differential sensing is also a field where synthetic receptors are being heavily exploited. This approach to sensing uses cross-reactive receptors, which necessarily lack high selectivity. Because synthetic receptors are routinely not nearly as selective as their biological counterparts, they are excellent for differential sensing purposes. **Anzenbacher** explored very small arrays of fluorogenic ligands for classifying different metals and then used one such array to fingerprint bottled water samples on the basis of metal content.[20] **Suslick** used amine-functionalized


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polymers with pH indicators to make a colorimetric array that quantitates formaldehyde over ppm to ppb concentrations.[21] **Bunz** and **Rotello** are moving the field toward biological applications and have shown that arrays of conjugated polymers can fingerprint and differentiate normal, metastatic, and cancerous cells.[22]

It is hoped that this compilation of a small fraction of the Articles and Communications related to molecular sensing published over the past few years in *JACS* will provide a peek at the diversity of approaches and applications of molecular sensors. The immediate future and the long term will bring additional supramolecular and reaction cascade innovations, as well as practical ramifications of the field of molecular sensing. The pages of *JACS* will therefore continue to hold many of the breakthroughs that will solve the diagnostic problems of the 21st century.

*Eric V. Anslyn, Associate Editor*

JA108349Y

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