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Editors Letter

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A Win for Bioorthogonal Chemistry

Through the *ACS Chemical Biology* Lectureship, the journal and the ACS Division of Biological Chemistry invite top-notch young investigators to share their research and honor one eminent chemical biologist. Past award winners include Professors Alanna Schepartz and Stuart Schreiber.[1] This year, the symposium was part of the 243rd ACS National Meeting held March 25−29, 2012 in San Diego, California. The recipient was Professor Carolyn Bertozzi from the University of California, Berkeley for her substantial contributions and seminal work in the chemical biology field. Coincidentally, Bertozzi also delivered the Kavli Foundation Innovations in Chemistry Lecture at the 243rd ACS National Meeting.

Program Chair, Dewey McCafferty and *ACS Chemical Biology* Editor-in-Chief Laura Kiessling presided over the *ACS Chemical Biology* Award Lecture and Symposium. As a prelude to the keynote lecture, emerging young investigators in the field presented their work. This year, Lei Wang, Dustin Maly, Douglas Weibel, and Minkui Luo delivered exceptional talks, building momentum to Bertozzi' s keynote address. This Editorial will briefly summarize the evening's presentations.

The incorporation of unnatural amino acids into proteins provides unique properties that have revolutionized biological studies. Kicking off this year's award session was Lei Wang from the Salk Institute, who spoke about the creation of an *Escherichia coli* strain that could completely recode the UAG stop codon into one that can incorporate unnatural amino acids at multiple sites. By significantly engineering an *E. coli* strain, Wang's group showed that Release Factor 1, which was previously thought to be essential for translation termination, was in fact dispensable by "fixing" a second translational factor, Release Factor 2. Using this strain, his group incorporated unnatural amino acids with a UAG-decoding tRNA-synthetase pair into multiple sites in different proteins.[2]

Small molecule inhibitors provide rapid, reversible, dose-dependent control over protein function. Dustin Maly, from the University of Washington, spoke about developing a general method for activating cell signaling enzymes using small molecules. Maly's group showed that a protein of interest can be engineered to include an autoinhibitory switch comprising the antiapoptotic protein Bcl-xL and the peptide BH3, which could subsequently be selectively controlled using a cell-permeable small molecule. This elegant methodology paves the way for more controlled regulation of enzymes involved in cell signaling.[3]

Osmotic pressure is a common feature associated with biological systems. In bacteria, peptidoglycan plays a significant role in resisting changes in osmotic pressure. Douglas Weibel, from the University of Wisconsin, spoke about his interest in understanding how bacteria resist large osmotic pressures. Weibel's lab built a small polymer "clamp" to measure the Young's modulus (E), i.e., stiffness of bacterial cells. Based on his measurements, for *E. coli* MG166 E = 50−150 MPa, for *Bacillus subtilis* E = 100−200 MPa, and for *Pseudomonas aeruginosa* E = 100−200 MPa.[4] This methodology provides an inexpensive and relatively simple method to measure the cell wall stiffness independent of shape or organism.

The human genome encodes over 60 protein methyltransferases (PMTs), most of which have not been well-described. The relatively few characterized PMTs display a variety of physiological and pathological functions. PMTs typically function as multimeric protein complexes with apparent promiscuous substrate profiles, i.e., one substrate target can be recognized by multiple PMTs. As a result, determination of the *in vivo* substrate of a PMT is challenging.[5] *S*-Adenosyl-L-methionine (SAM) is the cofactor PMTs use to transfer a methyl group to specific target proteins. Minkui Luo, from the Memorial Sloan-Kettering Cancer Center, described an innovative method by which a SAM analogue can be utilized in combination with engineered PMTs to identify cognate substrates of PMTs in a complex cellular milieu.[6]

While introducing the *ACS Chemical Biology* Lectureship winner, Kiessling lauded Bertozzi as a pioneer in the field who has shown the value of utilizing azides in probing the chemistry of a cell. Apart from being a great advocate for glycoscience and chemical biology, Bertozzi is an engaging teacher who has helped launch the academic careers of several former graduate and postdoctoral students. Of course, Bertozzi is best known for developing "bioorthogonal chemistry" reagents that have opened the door for studying biomolecules in cultured cells and live organisms.[7]

Taking the podium, Bertozzi delivered the award presentation, titled "Bioorthogonal Chemistry for Glycoprofiling and Beyond". The posttranslational modification formylglycine, found in the active sites of sulfatases, has orthogonal reactivity *via* an aldehyde group. This modification caught Bertozzi's attention, and her lab went on to describe the introduction of a genetically encoded "aldehyde tag" into recombinant proteins for site-specific labeling and bioconjugation *in vivo*.[8] This seminal application provided a simple way to incorporate bioorthogonal chemistry into proteins in a relatively "low-tech" way and was applied toward the site-specific modification of clinically important immunoglobulin G antibodies (IgGs) expressed in mammalian cells. The significance of this application is apparent given that immunoglobulin-based drugs are one of the fastest growing categories of biopharmaceutical therapeutics.[9] Redwood Bioscience, a biopharmaceutical company for the optimization of drug conjugates, is based on this concept. The aldehyde tag technology was also used to achieve precise protein glycosylation, a long sought after goal of biopharmaceutical companies.[10] Another application is the preparation of protein fusions for multidrug therapies. Bifunctional proteins are typically generated through genetic fusions, an often unwieldy approach. Recently, Bertozzi also described a method that exploits the aldehyde tag technology to produce protein−protein conjugates of unprecedented size and complexity.[11]

In conclusion, Professor Bertozzi's captivating talk demonstrated the enormous potential of the aldehyde tag protein modification toward the development of novel therapeutics,

Published: May 10, 2012

   dx.doi.org/10.1021/cb300211a | *ACS Chem. Biol.* 2012, 7, 781−782

which confirms the power of chemical biology in the production of next-generation therapeutics. *ACS Chemical Biology* and the Division of Biological Chemistry were pleased to facilitate this lectureship and session and look forward to sponsoring future award winners and symposia.

Jitesh Soares, Managing Editor, *ACS Chemical Biology*

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