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EDITORS LETTER

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Innovative Research at the Interface of Chemistry and Biology

An immensely popular symposium, the "Annual Frontiers at the Chemistry-Biology Interface" meeting, brings together the finest chemical biologists in the Mid-Atlantic region of the United States. Fittingly, this year the meeting was hosted by The University of Delaware, where Richard F. Heck produced pioneering research in palladium-based coupling reactions for stable carbon−carbon bond synthesis earning him the 2010 Nobel Prize for Chemistry. The symposium, chaired by John Koh, program director of the Chemistry-Biology Interface program at The University of Delaware, covered the wide array of topics constituting "chemical biology". This editorial gives a brief overview of the research presented at the meeting.

Observing rapid dynamics of protein folding is an important focus of research for biochemists. However, the relatively large size of the fluorophores currently in use hampers the resolution observed in these studies. To this end, James Petersson presented on reducing the size of fluorescence-quenching probes to increase spatiotemporal resolution when studying protein dynamics. Using *p*-cyanophenylalanine as a fluorophore and backbone thioamides as a small-sized fluorescence quencher, dynamic protein folding could be observed with superior resolution.[1]

The development of defined polyvalent conjugate vaccines from synthetic oligosaccharides and a recombinant "carrier" protein is a fairly new and potentially lucrative approach in vaccine design among carbohydrate chemists. Using this approach, Pumtiwitt McCarthy described some of her latest work at the FDA, which covered recent advances in developing a bioconjugate vaccine against meningitis and tetanus by chemoenzymatic synthesis.

Soluble guanylate cyclase is a multidomain 150 kDa enzyme that functions as a key receptor in the nitric oxide signaling pathway, which is crucial in regulating the cardiovascular system. To date, researchers have been able to determine the structure of individual domains of this large modular enzyme, but the structure of the complex remains elusive. Elsa Garcin, from the University of Maryland, Baltimore County, described some of the challenges facing her laboratory in determining the comprehensive structure of soluble guanylate cyclase.

Analogous enzymes are those that catalyze the same reaction using dissimilar active site structures. Ya-Ming Hou, from Thomas Jefferson University, provided a classic example of analogous enzymes when studying tRNA m1G37 methyltransferases, Trm5 and TrmD. By monitoring the kinetic and binding parameters of these enzymes, her group compared and contrasted the differing mechanisms by which these enzymes catalyze the N-methylation of tRNA at position G37.

The success of nonviral gene therapy is greatly dependent on the precision with which DNA is released in a localized area of a target cell. Acknowledging the importance of accurate release of DNA, Kory Blocker, from Millicent Sullivan's laboratory at the University of Delaware, spoke about newly developed methodologies for substrate mediated gene delivery. One such approach was the application of a peptide-nucleic acid based technology for the localized release of plasmid DNA in a cell, which has significant implications to a broad range of therapeutic applications.[2]

Figure 1. Trabant Center, The University of Delaware, site of the 2011 Annual Frontiers at the Chemistry-Biology Interface Meeting.

In his talk, Shuwei Li, from the University of Maryland, demonstrated the utility of using a novel methodology developed in his lab, *i.e.*, the use of a deuterium isobaric amine-reactive tag, for more accurate and cost-effective identification and quantitation of post-translational modifications by mass spectrometry.[3]

For the first time, this year's symposium featured a student-elected speaker at the meeting. Lynn Hyde, from Merck Research Laboratories, was the selected speaker. Her talk focused on elucidating a novel class of therapeutics that reduces β-amyloid peptide, the main component of amyloid plaques found in the brain, a well-established pathological feature of Alzheimer's disease. Specifically, her group identifies BACE-1 (human β-secretase) inhibitors, which lower β-amyloid peptide in the cerebro-spinal fluid and cortex of the brain.

The influenza A virus enters its target cell *via* endosomes. The low pH of the endosome triggers membrane-spanning A/M2 protein to pump protons into the virion. The resultant drop in pH causes the uncoating of viral ribonucleoprotein which is subsequently transferred to the cytoplasm of the cell and enhances its infectivity. Jun Wang, from William Degrado's laboratory at the University of Pennsylvania, spoke extensively on his research focused on structure-based drug development targeting this A/M2-proton channel with the ultimate goal of producing novel antiflu therapeutics.

MicroRNAs are key regulators of gene expression *via* translational repression and gene silencing. Pamela Green, from the University of Delaware, provided a powerful combination of sequencing and experimental procedures to complement computational methods for identifying and validating novel microRNA. These methods were used to identify microRNAs involved in the regulation of the stress response in higher plant systems.

Fragment-based drug discovery has emerged as a viable paradigm to identifying novel lead compounds. To this end, James Stivers from the Johns Hopkins University delivered a captivating talk on the role of linker strain when designing high-affinity inhibitors composed of two fragments that interact with two separate sites on a target enzyme.[4]

Thomas Stevensson, from DuPont, described his work in developing novel drugs using exhaustive structure−activity

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relationship studies. By taking a previously published method for synthesizing pyrazinones,[5] his team studied the structure−activity relationship of 600 related compounds to identify a compound that could one day potentially replace paclitaxel (commonly referred to as Taxol) as an anticancer drug. Like paclitaxel, the mechanism of action of this compound is to stabilize microtubules, which in turn interferes with normal cell division.

From new imaging tools, to chemical inhibitors elucidating enzyme mechanisms, to drug delivery systems, to the identification of innovative lead compounds for drug development, this year's Mid-Atlantic Annual Frontiers at the Chemistry-Biology Interface meeting provided a fascinating assortment of cutting-edge research in chemical biology and should be a fixture on any aspiring researcher's schedule in the region.

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