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EDITORS LETTER

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Honoring Stuart Schreiber

Each year the *ACS Chemical Biology* Lectureship honors the contributions of an eminent individual in the field of chemical biology. This year, the award recognizes the work of Professor Stuart Schreiber, Harvard University; Director of Chemical Biology and Founding Member of the Broad Institute of Harvard and MIT; and Howard Hughes Medical Institute Investigator; for the systematic application of small molecule probes to anticancer drug development (Figure 1). Schreiber made seminal contributions to the field of research we now refer to as "chemical biology", including identifying protein phosphatases (*e.g.*, calcineurin) and kinases (*e.g.*, mTOR) as important cancer drug targets and developing small molecule "dimerizers", which activate specific cellular signaling pathways with spatiotemporal control in animal models. His freely available database, ChemBank (http://chembank.broadinstitute.org), provides a comprehensive list of small molecule screening assays. This utility has been central to the identification of specific inhibitors to Hedgehog signaling in mammalian models. For more information on Stuart Schreiber, I invite you to visit the *ACS Chemical Biology* division Web site at http://divbiolchem.org/awards/recipients.

The Lectureship award was held as part of the 241st ACS National Meeting in Anaheim, California. In the jam-packed Marquis Ballroom at the Marriott Hotel, the event was part of the "Frontiers in Chemical Biology" symposium organized by Joseph Bollinger and Laura Kiessling, the Editor-in-Chief of *ACS Chemical Biology*. The session showcased top-notch emerging investigators and highlighted a broad overview of research on the frontiers of chemical biology.

The symposium commenced with James Chen, a former graduate student of Schreiber and a current faculty member at Stanford University. He introduced the subject of small molecule modulation of stem cell differentiation, and his talk covered some of the latest chemical technology developments in studying the underlying mechanisms of embryogenesis in a zebrafish model.[1] Chen spoke about the use of "caged" morpholino-based compounds to study the role of genes in zebrafish with spatiotemporal precision.[2] Next, Danica Fujimori from the University of California San Francisco covered the exciting field of RNA methylation by radical *S*-adenosylmethionine-dependent enzymes, RlmN and Cfr. To gain mechanistic insight into the functioning of these enzymes, Fujimori's group utilized sophisticated deuterium labeling experiments to elucidate a novel and elegant mechanism. These studies indicated that these enzymes function as methyl synthases rather than methyl transferases.[3] In an independent study, Squire Booker's group has also recently reported a similar mechanism for RlmN and Cfr function.[4] Hening Lin from Cornell University described the discovery of novel roles for sirtuins, which are typically known to post-translationally deacetylate lysine residues in proteins in an NAD-dependent reaction. A key finding was the ability of one such sirtuin, SIRT5, to post-translationally desuccinylate and demalonylate proteins. Lin also noted the influence of Schreiber's research on his current work when he highlighted Schreiber's discovery of histone deacetylases, which led to the discovery of sirtuins in a cell by Leonard Guerante. Ulrike Eggert from Harvard Medical School has been developing novel approaches, such as the use of specific chemical inhibitors to study the link between lipids and cytokinesis.[5] In an exciting talk, Eggert described the use in her laboratory of a multifaceted approach to characterize an association between ceramides and cell division. In her seminar "Painting the Cysteine Chapel", Kate Carroll from the Scripps Research Institute outlined the evolving view on the role of hydrogen peroxide in a cell, specifically its modulation of cysteine oxidation to sulfenic acid in proteins of clinical importance.[6] Additionally, Carroll described recently developed methodologies for monitoring sulfenic acid formation and profiling the "sulfenome".[7]

Figure 1. Stuart Schreiber receiving the 2011 *ACS Chemical Biology* Lectureship award from Editor-in Chief Laura Kiessling. Image credit: Jitesh Soares.

In her introduction of Schreiber, Laura Kiessling honored him as the pioneer of "chemical biology" who extended the reaches of chemistry to other scientific fields. Taking the podium, Schreiber focused on bridging the gap between small molecule probe research and cancer. Describing cancer as a "genetic disease", he outlined how his work at the Broad Institute aims to comprehensively understand the genetic features of human cancers and drug efficacies of identified compounds. He cited the example of the well-established, genetically matched drug imatinib and stressed the need for connecting genetic features of the tumors to compounds that specifically act on the acquired oncogene or the resultant cancer pathways.[8] An oncogene currently at the forefront of drug development in cancer therapy is the mutated encoding gene of isocitrate dehydrogenase, which is implicated

Published: May 20, 2011

in 70−80% of human brain cancers. The oncogene variant of isocitrate dehydrogenase, *e.g.*, IDH1-R123H, has an alternate enzymatic activity that results in the deleterious production of R-2-hydroxyglutarate in addition to reducing the normal activity of isocitrate dehydrogenase in a cell. The development of a specific compound to inhibit this alternate pathway is currently a key area of research for treating brain cancers.

Schreiber characterized the screening and identification of potentially therapeutic compounds as relatively facile and opined that the real difficulty in cancer drug development is assay development and the chemical biology needed to turn promising molecules into successful therapeutic agents. Today, among all the potential therapeutic compounds identified, only ∼300 of these small molecules have been stringently characterized as sufficiently specific to minimize broad, deleterious side effects.

In his concluding remarks, Schreiber stressed the need for creative new ideas in cancer drug development. Intelligent, systematic use of chemical biology is at the forefront of this search. Congratulations Professor Schreiber and thank you.

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