Editor's LETTER

ACS chemical biology

Time to Think

Here is Edward Bear, coming downstairs now, bump, bump, bump, on the back of his head . . . It is, as far as he knows, the only way of coming downstairs, but sometimes he feels that there really is another way, if only he could stop bumping for a moment and think of it.
—A. A. Milne, Winnie-the-Pooh

For scientists, time to evaluate research directions and consider new ones seems only too rare. The beginning of the new year provides an opportunity to stop all that bumping and think. In this spirit, we thought it appropriate to review some dynamic areas of chemical biology—because they are spawning new and important results and have tremendous potential for continued growth.

To many researchers, the field of chemical genetics, in which small molecules are used as probes of biological processes, is synonymous with chemical biology. Although we at *ACS Chemical Biology* have a broader definition, we recognize that chemical genetics is an integral and exciting component of the field. A key aspect of chemical genetics is the identification of small molecules that can perturb a biological target or process of interest. Such small molecules typically are identified *via* high-throughput screening. With increased access to high-throughput screening equipment for industrial as well as academic researchers, new applications of small molecules are emerging. In this issue, David Spring and colleagues review (p 24) two strategies for identifying bioactive small molecules: small-molecule microarrays and high-content screening. Small-molecule microarrays provide a simple means of probing receptor–ligand interactions. With regard to high-content screening, it is clear that innovations in data analysis and processing will continue to emerge; consequently, the applications of high-content screening will multiply. In addition to this Review, three commentaries address the mechanics of performing a chemical screen in the laboratory (p 9) and describe how two chemical screening centers, one at a university (p 17) and one at a research institute (p 21), operate and serve their communities. Together, these contributions cover key aspects of ligand discovery.

High-content screening relies on the development of new methods to visualize proteins or ligands in live cells. The Review by Kai Johnsson and Nils Johnsson (p 31) emphasizes recent chemical strategies to image biological processes. To this end, they describe several methods to follow protein localization in time and space. These approaches focus on using protein fusions such that the fusion can undergo rapid reaction with a fluorophore equipped with a reaction group (organic or inorganic) to transfer a label to the protein of interest. In their Review, they mention the importance of reaction kinetics, which in turn dictates the concentration of reactive fluorophore that must be present to achieve effective labeling. This issue of kinetics is also critical for chemical sensors, because it will determine their sensitivity. As discussed in the Review, the sensors for ions, such as Zn^{2+}, or transient signaling molecules, such as NO, often are based on metal complexation. Because complexation can be rapid, sensors based upon it can have the high sensitivity required. These examples underscore the importance of inorganic chemistry to chemical biology. The advances in biomolecular imaging discussed indicate the vital contributions of chemical biology to this important area.

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We have included a Review focused on the use of single-molecule experiments to elucidate biological mechanisms (p 53), which is synergistic with the Review (p 31) describing biomolecular imaging; both describe advances that allow scientists to answer new types of mechanistic questions. Peter Cornish and Taekjip Ha provide an overview of single-molecule techniques that highlights several applications focused on illuminating catalytic processes such as transcription, myosin VI movement, and glycosidase activity. These studies, along with the examples addressing protein folding, provide powerful illustrations of how analysis of single molecules can afford new insights. In the final section of the article, the authors presage future directions for the field. It is clear from this section, as well as the rest of the Review, that chemical biology will not only benefit from single-molecule studies but also facilitate them by providing valuable new tools for conducting new types of studies.

Mass spectrometry (MS) is another technique that is revolutionizing the study of biological systems. Indeed, many chemical biology approaches rely on MS to identify target proteins or to quantify the effects of chemical perturbants on the levels or modification states of proteins (or metabolites) within a biological system. Natalie Ahn and colleagues provide an overview (p 39) of recent advances in using MS for protein profiling. They evaluate the strengths of the strengths and weaknesses of state-of-the-art methods for accumulating and analyzing MS data. In addition, they offer an outlook for future advances. Because MS is such a widely used tool and because this field is highly dynamic, this Review will provide chemical biology researchers with guideposts for choosing and applying different MS methods.

Anna Mapp and Aseem Ansari (p 62) return to the theme of using small molecules to effect changes in biological systems. They focus on using design principles to mimic the proteins that regulate the complex process of transcription. The 2007 Nobel Prize in Chemistry highlighted how atomic-level views of transcription are illuminating the process. Mapp and Ansari suggest ways in which new insights into transcriptional regulation can be used to generate small-molecule regulators. Because many transcriptional regulators are modular proteins, small-molecule building blocks can be used alone or in combination to block or promote the assembly of different multiprotein assemblies. Such assemblies can be used to illuminate the roles of different complexes in transcription or to explore and exploit the consequences of altering gene expression. Although RNA interference is a powerful general method for inhibiting the production of target proteins, assessing the consequences of up-regulating the production of a specific protein is more difficult. Artificial transcription factors can address this deficiency. Their potential to exert temporal control over transcription is another benefit. The summary outlining the different modes by which transcription is regulated provides fodder for those interested in designing artificial transcription factors and accentuates the utility of such compounds for probing biological systems.

We plan to provide our readers with additional Reviews throughout the year. If there are specific Reviews that you wish to submit to the journal or topics you would like to see covered, please email us at chembiol@acs.org. Lastly, we hope that the new year brings you ample time to think.

Laura L. Kiessling
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