Editor's LETTER

ACS chemical biology



# Reflections on Chemical Biology

Although we still consider *ACS Chemical Biology* as being a young journal, we do already have our traditions and rituals. One of these is to invite, once per year, scientists from various areas of chemical biology to reflect on progresses achieved and to define the challenges that lie ahead. While we try to group these reviews around a common theme, the diversity of chemical biology as a discipline and the divergent opinions and preferences of our editorial board help us avoid the compilation of a thematically narrow special issue (*vide infra*).

The main focus of this year's special issue is the use of small molecules as probes to interrogate signaling pathways and the identification of the target proteins of such probes. Virtually all biological processes are controlled by protein phosphorylation and protein kinases, a research topic that has consequently attracted numerous chemical biologists. Through this work it has become apparent that a variety of complementary tools are needed so that we can unravel all the mysterious mechanisms of how kinases control signaling networks. In this issue, Carlson and White provide an overview of how recent developments in chemical phosphoproteomic and chemical genetic methods permit us to gain new insights into network structures and the system-wide effects of kinase inhibitors. The authors predict that such approaches will lead to a much more detailed understanding of signaling networks regulation and how these networks respond to targeted perturbations, which should ultimately also lead to more efficacious therapeutic strategies.

Small molecule probes are often generated through screening for molecules that either directly target defined biochemical activities (proteins) or induce complex phenotypes. Ulrike Eggert now argues in her review that there is plenty of room in the middle: The screening for pathway-directed probes should bridge and complement approaches that either target individual proteins or complex phenotypes. Her review not only demonstrates how such molecules can be identified but also outlines the enormous promises they hold.

Small molecules generally exert their activity by binding to individual proteins, and the identification of all protein targets of a given bioactive molecule or drug is one of the key challenges in chemical biology. Two articles in this issue describe complementary approaches to address this problem. Jing Huang and colleagues review methods for the direct identification of drug–protein interactions. At the center of their review is a recently introduced approach (dubbed DARTS) that exploits the phenomenon that the binding of small molecules to proteins often increases their resistance toward proteases. The key feature of this approach is that it does not require a derivatization of the molecule of interest. Palchaudhuri and Hergenrother describe how transcription profiling and RNA interference can be used to define the mechanism of action of a small molecule and to identify new therapeutic use. As with DARTS, these approaches do not require a modification of the small molecule of interest and have the additional advantage that they are compatible with membrane proteins. The Palchaudhuri and Hergenrother review is complemented by a careful analysis by Sigoillot and King of how RNA interference screenings can be compromised by the occurrence of unintended off-target effects. The authors consider the potential causes of off-target effects and why this phenomenon can produce high hit rates in siRNA screens. The review is a reminder also that results obtained with Nobel-prize-winning technologies require independent validation before new biological insights can be gained.

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Finally, chemical biology not only relies on small molecules but often utilizes protein engineering to create powerful reagents for mechanistic and therapeutic applications. In this issue Urban and Merten discuss the use of retroviral display as a platform for the presentation of correctly folded and post-translationally modified proteins on cell plasma membrane-derived particles. The technology is a welcomed addition to the toolbox of protein engineers and should become important both for medical applications and for the engineering of mammalian proteins in general.

I hope you will find this collection of timely reviews as stimulating as I do, and I wish you an uninterrupted reading.

Kai Johnsson
Member, *ACS Chemical Biology* Board of Editors