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Editors Letter

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Chemical Biology − Current and Next Challenges

In August 2012, I not only turned 40 years old, I also became an Associate Editor for *ACS Chemical Biology*. So far it has been a fantastic and inspiring time serving this esteemed journal. I would like to take the opportunity and thank all authors for their exciting contributions and the referees for returning their reviews on time!

This being said, the exciting advances in chemical biology and its related disciplines stimulate the editors of *ACS Chemical Biology* to once a year invite scientists from diverse areas of chemical biology to reflect and highlight current and next challenges in the field. The main focus of this year's special issue is on enzymes that are considered to be difficult to target and translational chemical biology to convert basic research into clinical applications. Interdisciplinary science and particularly the treasures, which lie not only at the interface of chemistry and biology but also medicine, puzzle me since I started my independent research career. In my daily research, exciting collaborations arise with clinicians and scientists in the era of cancer genomics. Chemical biology approaches to support target identification and target validation enable us to assist in the translation of genomics discoveries into clinical trials.[1] Stimulated by this, I am confident that applied basic research in the area of chemical biology will also have an impact in overcoming some of the challenges in modern drug discovery and medicinal chemistry.[2]

In this special issue, Matthew Cooper and Bern Becker highlight aminoglycoside antibiotics and provide a perspective on how this "old class" of drugs and a more comprehensive understanding about their mode of action may help us to battle the dramatically increasing rate of infections caused by multidrug-resistant pathogens, particularly Gram-negative bacteria.[3] Enzymes with relevance to infectious diseases but also cancer are the focus of the Yves Pommier's review on drugging topoisomerases.[4] This ubiquitous class of enzymes controls DNA supercoiling and entanglements and is essential for the orchestration of transcription and replication in every cell. Pommier highlights on "interfacial inhibition" by which topoisomerase-targeted drugs trap protein−DNA complexes rather than inhibiting the enzyme in a classical manner. This exciting mode of action might very well serve as a generic strategy for also targeting transcription factors. Targeting enzymes by transition state analogs has long been in the focus of Vern Schramm's research. In his review "Transition States, Analogues, and Drug Development", he underscores how transition state analogues convert the short-lived transition state to a stable thermodynamic state to eventually result in high affinity binders.[5] Understanding this fast dynamic process requires the combination of kinetic isotope effects and computational chemistry and may foster the design of novel transition state analogs.

Two reviews in this issue focus on protein kinases. Zhizhou Fang, Christian Grütter, and myself focus our review on allosteric kinase modulation and describe how exclusive structural features can be successfully exploited for the selective regulation of kinases by small molecules. Such allosteric modulators and their future development offer exciting strategies to explore kinase function beyond catalysis.[6] In the second review, Philip Cohen and Dario Alessi report on what is next in kinase drug discovery. While kinases related to cancer continue to be the center of inhibitor research, targeting protein kinases for the control of the immune system as well as hypertension and Parkinson's disease will witness a surge of interest over the next decade. The authors also highlight that pseudokinases are an unexplored area with high relevance for both chemical biology and for drug development respectively.[7] Protein phosphatases reset kinase function, and their protective and promoting roles in the etiology of diseases have long been the focus of chemical biologists and the pharmaceutical industry. Sofie De Munter, Maja Köhn and Mathieu Bollen highlight current strategies not only for the development of inhibitors but also for development of activators of protein phosphatases. The authors conclude that it is feasible to design potent and selective protein phosphatase modulators with therapeutic potential.[8] "Fat Chance! Getting a Grip on a Slippery Modification," is the title of a fantastic review by Christopher Tom and Brent Martin and deals with protein palmitoylation.[9] This post-translational modification is key for the localization, trafficking, and compartmentalization of protein function. The development of powerful chemical tools and technologies help studying the pervasive role for palmitoylation across the eukaryotic kingdom and dissecting the dynamics of the acylation cycle. Proteolysis is another post-translational modification with high clinical relevance. Markus Kaiser, Michael Ehrmann, and colleagues report on the diversity of allosteric regulation of proteases. The detailed understanding of the structural and functional features of allosteric regulation offers unique opportunities for functional protease modulation in the development of chemical probes and drug discovery.[10]

Finally, targeting of protein−protein interactions continues to be one of the most exciting but also difficult fields in chemical biology and drug discovery. The 14-3-3 proteins represent a wealth of known protein−protein interaction partners associated with a wide array of biological processes and diseases. Christian Ottmann and Luc Brunsveld summarize in their review recent success stories in the development of both small-molecule inhibitors and stabilizers of protein−protein interactions mediated by 14-3-3 proteins.[11] These case studies impressively show alternative concepts for addressing enzymes and protein functions that are difficult to target by small molecules.

I hope you enjoy reading these reviews and that they will inspire you on your way of translating basic chemical biology research.

Daniel Rauh, Associate Editor, *ACS Chemical Biology*

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