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Activity-Based Protein Profiling

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Preface

Activity-based protein profiling (ABPP) is a chemical proteomic technology that applies the fundamental principles of chemistry for the global analysis of protein function and small molecule interactions in native biological systems. A large fraction of the proteome remains functionally unannotated, and an even smaller portion has selective small molecule probes for pharmacological characterization. ABPP addresses these challenges by deploying broadly reactive chemical probes to interrogate functional and druggable sites on many proteins (100s–1000s) in parallel. These profiles can furnish novel insights into protein function, as well as hit compounds for selective chemical probe development against a wide array of proteins. The power of ABPP thus lies in its multidisciplinary nature that can seamlessly bridge basic protein function with the translational potential afforded by modern synthetic and analytical chemistry methods. This volume provides a focused collection of recent developments that highlight the merits and opportunities of using ABPP for biological discovery.

The first half of this volume focuses on using ABPP to illuminate functional alterations in bacterial proteomes during the formation of microbial communities and in response to host–pathogen interactions. In the first chapter, Wright and Whidbey describe how ABPP can be implemented to study alterations in protein biology as bacteria interact with each other and respond to environmental changes as exemplified by the microbiome. Carlson and colleagues follow with a detailed overview of chemical probe design, applications, and proof-of-concept examples for the application of ABPP in prokaryotic systems. Seeliger and colleagues describe ABPP's utility in the understanding of immune evasive strategies of mycobacteria, with emphasis on serine hydrolase and kinase activities involved in metabolic reprogramming of these bacteria during the transition toward a persistent dormant state. The next set of chapters shift focus toward changes in proteome activity related to host–pathogen interactions. Hatzios and colleagues provide a synopsis of several in vitro and animal microbial infection models where ABPP has the potential to discover new antibacterial targets and corresponding lead inhibitors. Hang and Peng describe the use of ABPP to exploit a specific metabolic vulnerability of pathogenic bacteria and fungi. Specifically, protein fatty acylation of both

host and bacterial proteins is important for survival and pathogenesis, and inhibitors that block these fatty acylation pathways may lead to new antimicrobial and antifungal strategies. Ovaa and colleagues present another strategy for targeting bacterial and viral effector proteins through perturbation of ubiquitin signaling pathways that regulate protein homeostasis in pathogen and host cells. Pezacki and colleagues provide specific examples of applying ABPP for targeting host–virus interactions, while Child and Tate focus on applications for the study of parasites. Finally, Hsu and colleagues put forth a general overview of ABPP to study the regulation of T cells, a key immune cell subset for immunity against pathogens as well as cancer.

The second half of the volume focuses on new enabling tools for ABPP investigations of protein biology including posttranslation modifications (PTMs), protein–protein interactions, and protein–small molecule interactions. Cohen and colleagues summarize the use of ABPP to study and target poly-ADP-ribose polymerases (PARPs), which are key enzymes that regulate ADP-ribosylation signaling in cells. Thompson and colleagues describe ABPP to study protein citrullination, an unusual PTM resulting in the conversion of arginine residues into citrulline that is important for apoptosis, terminal differentiation, and transcriptional regulation of autoimmune disorders. Verhelst and colleagues shift from PTM analysis to enzyme subclasses under investigation by ABPP, specifically, the use of ABPP for the development of selective inhibitors against proteases that contain highly similar active sites. van der Stelt and colleagues tackle lipid enzymes, which present different challenges that can be addressed by ABPP including assaying integral membrane enzymes without the need for purification. Considering that proteins do not function in isolation, Kakeya and Ishikawa describe the application of ABPP for studies of large multidomain protein complexes known as non-ribosomal peptide synthetases (NRPS). NRPS systems are a rich resource for the discovery of new antibiotics, and ABPP can provide fresh insights into the protein machinery required to harness their synthetic potential. As an appropriate follow-up to the discussion of natural products, Nomura and Maimone describe mining natural product structures for electrophilic scaffolds that can be converted into new ABPP probes for protein and inhibitor discovery. Backus concludes the volume with a provocative overview of the growing number of functional and druggable sites on proteins being revealed by ABPP through, for instance, global assessments of cysteine reactivity in biological systems.

In summary, ABPP has emerged as a fundamental technology for the functional analysis of proteins in native biological systems. Ranging from studies of protein activity and posttranslational regulation to protein–protein and protein–small molecule interactions, ABPP is enabling chemists and biologists to address important basic and translational research problems that have been historically beyond the reach of more conventional methods. The chapters in this volume

collectively exemplify the exciting diversity of approaches and applications of ABPP, with a common theme of enabling new opportunities for discovery in the fields of microbiology, immunology, and beyond.

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