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Cell Chemical Biology

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Editorial

Chemical Tools in Biological Discovery

We are excited to welcome you to our special issue on Chemical Tools in Biological Discovery. The past few decades have given rise to exciting developments in the field of chemical biology. Advancements in biochemical techniques and analytical instrumentation, the ability to collect and access large amounts of "big omics data" (including genomics, transcriptomics, proteomics, and metabolomics), and innovations in bioinformatic analyses have catalyzed the development and application of chemical tools for interrogating biological systems. These chemical tools have enabled the visualization of biomolecules in live cells and single cells, the regulation of cell-signaling networks, the identification of therapeutic targets, and the development of small-molecule drugs for a wide range of diseases.

In this special issue, we aim to highlight a few of the key advances in chemical-tool development and the fundamental biological insight gained with the advent of these tools. The 15 articles included within this issue highlight innovations in the development of chemical probes for imaging, activity-based protein profiling, and pharmacological perturbation of biomolecules.

Chemical probes are critical to biological imaging, and three review articles and one resource article in this special issue focus on recent advances in imaging tools. Focusing on imaging RNA in live mammalian cells, Palmer and colleagues provide an overview of current technologies for elucidating RNA dynamics, localization, and function. Love and Prescher summarize advances in bioluminescence technology, with a special focus on the merging of bioluminescence with optogenetics to not only sense, but also control biological processes. Lanthanide luminophores exhibit numerous beneficial properties for biological imaging, including long-lived photoluminescence and large Stokes shifts. The unusual levels of sensitivity and multiplexing offered by lanthanide-based probes are discussed in depth in a review article by Cho and Chen. Lastly, in a resource article, Lavis et al. develop photosensitizers based on a rhodamine scaffold for a variety of applications, ranging from high-resolution imaging to the targeted destruction of proteins.

In addition to imaging, chemical probes provide greater insight into protein function and serve as pharmacological modulators and activity-based probes. Five review articles and three resource articles highlight chemical probes that aid in modulating and interrogating protein function. A review by Bogyo et al. focuses on the application of activity-based probes for investigating the serine hydrolase family of enzymes. Wang and Cole summarize the field of lysine posttranslational modifications (PTMs), with a focus on small-molecule probes and protein chemistries that have facilitated the characterization of writers, erasers, and readers of these PTMs. An important criterion for chemical-probe development is the ability to analyze endogenous proteins under native conditions. Hamachi et al. focus their review on the various chemical approaches for investigating native protein function, including ligand-directed chemistry for protein-selective labeling, activity-based protein profiling, proximity-dependent proteome labeling, and conditional proteomics. Although there are many established approaches for identifying selective and potent chemical probes, proteins that are highly dynamic in nature have traditionally been intractable targets. Garlick and Mapp discuss screening approaches for identifying small molecules with affinity to these highly dynamic protein targets. In addition to modulating protein function through direct inhibition or activation, small molecules can exert a biological outcome by inducing degradation of a target protein. In a review by Crews et al., key advancements in the rapidly growing field of targeted protein degradation and the PROteolysis TArgeting Chimera (PROTAC) technology are presented. Three resource articles within this issue underscore the utility of chemical probes for investigating protein function. Niethammer et al. developed a minimally invasive photoaffinity probe that enables the identification of ATP-interacting proteins within cell lysates, including previously unannotated ATP interactors. Maly et al. describe a chemoproteomic platform for determining changes in protein structure and dynamics upon small-molecule binding and apply this platform to demonstrate how conformation-selective Src kinase inhibitors differentially affect the local and global protein structure. Lastly, Fiedler et al. develop affinity reagents for identifying the interactome of inositol pyrophosphates, a complex family of phosphorylated metabolites with important biological functions.

The last three review articles discuss how chemical tools and methods have facilitated discovery within specific biological areas. Schultz and colleagues focus on pancreatic islet function and knowledge gained within this field through application of small-molecule and genetically encoded tools. Suga et al. discuss thiopeptides, with a focus on their biological activities, biosynthetic pathways, and engineering approaches to reprogram the structure and function of this important class of natural products. Lastly, Grimes et al. discuss how chemical and biochemical tools have been employed to study bacterial cell-wall biogenesis, resulting in the discovery of cell-wall interacting proteins, flippases, and cell-wall stoichiometry.

As is apparent from the descriptions above that chemical tools and the biological problems they address are highly diverse. Importantly, these tools are rapidly evolving with improvements in the sensitivity of analytical instrumentation, accessibility to large omics data, and computational capabilities. We are excited about the continual evolution and the increased adaptation of chemical tools by a wide range of researchers within chemical, biological, and clinical fields. *Cell Chemical Biology* will continue to bring attention to the rapidly developing area of chemical biology and highlight significant technical advancements in chemical probes, tools and technologies, analytical platform development/application strategies, and computational algorithms or major informational databases that are of value and interest to our broad readership, through our resource format.

As new tools emerge, we expect to see continued interest in the application of chemical biology tools and technologies among diverse group of researchers, from molecular biologists

to clinicians. At *Cell Chemical Biology*, we remain strongly interested in original research and resources/technology in addition to review articles encompassing diverse research areas. As a journal, we strive to promote diversity not only within the scientific topics we cover but, more importantly, within the larger community encompassing our own editors, authors, reviewers, advisory board members, and readers. We value how a community with diverse scientific expertise, gender, ethnicity, and geographic location stimulates scientific innovation. We are committed to fostering diversity in our advisory board and reviewer pool, and we are hopeful that the greater chemical biology community will join us in these efforts.

Finally, we would like to thank all the authors who contributed to this special issue, the reviewers who provided many valuable comments, and our diverse chemical biology community for continued support. We recognize the ongoing challenges of COVID-19 that our researchers are encountering, and we would like to assure you that we are flexible with the timing for revisions and encourage you to contact us to discuss any matter. Lastly, we invite you to read this special issue and share your latest and greatest chemical biology stories with us.

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https://doi.org/10.1016/j.chembiol.2020.08.004