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Preface

Chemical proteomics

Organic chemists have always been attracted to the chemistry of life. Synthetic organic chemistry of old has pursued the synthesis of natural products—the more complex, the better. Bioorganic chemistry in turn aims at unraveling the mechanism by which natural compounds are prepared in biosynthesis pathways, thereby seeking a molecular understanding of what makes life tick. Both synthetic organic chemists and bioorganic chemists however devote time on research that, though dealing with biological phenomena, is executed in the familiar environment of synthetic chemistry laboratory equipment. With the emergence of chemical biology research however this has drastically altered. Organic chemists have stood up that bring their creativity in chemical transformations to the complex, in terms of mixture of reactants, world of live. Selective organic transformations are now aimed for to occur in cell extracts, in living cells and even in living animals.

A research field that has in particular benefited from the interest of organic chemists is that of proteomics research. Proteomics research aims at providing a detailed insight in protein expression levels and how these differ between biological samples as a consequence of, for instance, disease states. Despite massive research efforts world-wide and impressive technological developments in analytical chemistry (in particular, mass spectrometry) in the past decade, to date it is near impossible to accurately map any and all proteins that are expressed at a given time in for instance a eukaryotic cell. There are simply too many different proteins, and the difference in the number of copies expressed between the least- and the most abundant proteins is simply too large to enable global analysis. Rather, efforts are directed to reduce the complexity of protein mixtures, and it is here that the field of chemical proteomics comes into play. In what has become known as activity-based protein profiling, covalent and irreversible inhibitors are equipped with affinity- or reporter tags. These activity-based probes are designed such that they react with a subset of a given proteome only, allowing for their enrichment and subsequent careful analysis. Protein families targeted by activity-based probes are normally enzymes and in this way a proteome is not only reduced in complexity but at the same time activity-based probes report on enzyme activity, and not mere protein expression levels. ABPP finally has proven to be of great use in the assessment of activity and selectivity of enzyme inhibitors as potential leads for drug development. A selective and cell-permeable enzyme inhibitor itself in turn may be used as a chemical genetics tool to selectively downregulate (through inhibition) of the enzyme activity at hand. Another area of research with high impact on chemical proteomics is that of modified metabolite labeling. In this research, a modified metabolite is equipped with a physiologically inert, small tag (normally azide or alkyne), which may end up in, for instance, a protein post-translational modification. In a bioorthogonal reaction the tag is then made to react with a complementary reactant, which in turn is connected to for instance biotin for identification and enrichment. Bioorthogonal chemistry in turn connects to activity-based protein profiling in the design of two-step activity-based probes. With these in the first step the proteins of interest are covalently modified, after which in the second step the modified proteins are bioorthogonally connected to the affinity/identification/enrichment tag.

This Bioorganic and Medicinal Chemistry special issue on Chemical Proteomics brings a choice selection of chemical biology research, with a special focus on the development and application of research tools designed by organic chemistry for chemical proteomics research purposes. Two timely reviews are devoted to subjects that need special attention from organic chemists in order to further the field of chemical proteomics research. Meijler and co-workers present an overview of the current state-of-the-art of photo-activatable probe development, an area of activity-based protein profiling of prime importance given that many enzyme families and most proteins without an enzymatic activity do not possess an amino acid side chain nucleophile conveniently there to react covalently with an activity-based probe. Wagner and co-workers in turn review recent literature dealing with the development of mild, chemoselective cleavable linkers, yet another area of research where organic chemistry may have great impact on chemical proteomics research. A considerable number of original papers discuss the design and application of activity-based probes. Sieber and co-workers bring a new study on the development of beta-lactone-based viral protease (ClpP) inhibitors. Van der Hoorn and co-workers bring two papers on ABPP of plant metalloproteases and serine hydrolases, respectively, and plant serine hydrolase ABPs are also the subject of a contribution from Kaiser and co-workers. Kim and co-workers demonstrate the usefulness of ABPP to reveal enzyme specificity of a given pharmacophore by the development and application of a proteasome subunit-specific (beta1i) probe. Tate and co-workers report on a series of cysteine protease ABPs with which the formation of the *Clostridium difficile* can be disturbed. Sewald and co-workers describe the application of quinone methide methodology to covalently trap bacterial aryl sulfatases, whereas lipase ABPP is the subject of the contribution of Birner-Gruenberger and co-workers. Verhelst and co-workers finally report on the development of the isocoumarin scaffold to arrive at two-step serine protease ABPs.

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The remainder of the contributed studies entails subjects varying from enzyme inhibitor development, bioorthogonal chemistry and modified metabolite labeling. Bleriot and co-workers describe the development of D-*manno*-configured azepanes as a new class of glycosidase inhibitors. Hang and co-workers apply bioorthogonal chemistry to specifically enrich for fatty acid modified proteins. Strain-promoted alkyne–azide click chemistry is the subject of both the study contributed by van Delft and co-workers and van der Linden et al., the former in a study in which the merits of this bioorthogonal reaction together with a mild, hydrazine-cleavable linker is evaluated, and the latter in a bid to reveal the extend of bioorthogonality of cyclooctyne-based click reactions set against the Staudinger–Bertozzi ligation. Burkart and co-workers report a new strategy for the detection of acyl carrier protein interaction networks based on covalent modification of acyl carrier proteins. Finally, Winssinger and co-workers describe the design of a series of biotinylated deguelin derivatives, and their use in probing the subcellular interaction partners of the potent cytotoxic agent, deguelin.

Altogether this special issue brings a nice overview of the current state-of-the-art of organic chemistry driven chemical proteomics research, with a special focus on activity-based protein profiling. The biological world to uncover with chemical proteomics research is large and yet at the same time it is clear that there is ample room for improvement in the development of tools and techniques, for instance with respect to bioorthogonal chemistry and cleavable linkers, but also in selectively addressing proteins other than enzymes in complex biological samples. I sincerely hope that this special issue will contribute to attracting researchers to the exciting field of chemical proteomics research.

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