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How to cite

WINSSINGER, Nicolas. Bioorthogonal Chemistry. In: Chimia, 2018, vol. 72, n° 11, p. 755.

This publication URL: https://archive-ouverte.unige.ch/unige:116258

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Nicolas Winssinger

An ideal bioorthogonal reaction is one that neither interacts nor interferes with a biological system of interest, be it a protein, a lysate, a live cell or a whole organism. Yet, the reaction should proceed under biocompatible conditions and at a rate that allows reasonably diluted conditions. These stringent demands have spurred the creativity of chemists resulting in a growing toolbox of transformations that enable practitioners to functionalize, crosslink or uncage biomolecules with an increasing degree of precision and control. The field has grown tremendously over the past two decades and this series of accounts and perspectives highlights areas of interest and emerging topics.

The ability to tag and modify proteins or nucleic acids lies at the core of chemical biology and biomedical research. The development of efficient, chemoselective ligation reactions using unprotected peptide fragments has propelled protein synthesis and enabled access to labelled or post-translationally modified peptides and proteins. At the nucleic acid level, novel technologies enable the functionalization or modification of RNA. Sensing oligonucleotides has also benefited from bioorthogonal reactions that are templated by specific DNA or RNA sequences, offering a rapid and enzyme free detection for imaging and diagnostics. Another area which has seen formidable advances in the past decade is bioorthogonal uncaging reactions to unmask a specific function. These advances are particularly relevant to the field of antibody-drug conjugates (ADC), with the aim of chemoselectively uncaging a cytotoxic drug strictly in an area of interest. The search for new reactivities has also instigated important developments in transition-metal catalyzed bioorthogonal reactions. While transition metals were too often perceived as toxic in cellular biology and sensitive to poisoning of their catalytic activity, there is now a growing number of catalysts which have been shown to operate in cellular context or even enrich in specific organelles, bringing the power of their unique reactivity to chemical biology.

Light has long been recognized as an attractive external stimulus to trigger a reaction since it can be controlled both in time and space. While photo-crosslinker have been used for nearly half a century, recent developments tuning the reactivity and physical properties of photo-crosslinker are extending the scope and utility of this technique which is quintessential to freeze dynamic interactions between partners. Other developments in the area have also delivered powerful ways to achieve a conjugation to a biomolecule with light.

Super-resolution microscopy has allowed us to see what was fuzzy just ten years ago. Developments in the area have benefited from photochemically active fluorophores that display changes in their photophysical properties upon irradiation with light. Notwithstanding these achievements, there are still many features of fluorogenic probes that could further enhance super resolution imaging. Fluorophores designed to spontaneously blink or designed to be photoswitchable and their incorporation into reporters or sensors will clearly bring further enlightenments.

There is no doubt that the growing toolbox of bioorthogonal reactions has empowered chemical biology and biomedical research. I wish to express my gratitude to the authors who have offered authoritative opinion on a number of frontiers in bioorthogonal chemistry. It is also evident from these opinion pieces that there is still much more to come in this exciting area of science.

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The Editorial Board of CHIMIA warmly thanks Prof. Nicolas Winssinger for his efforts in the planning and successful realization of this interesting and topical issue on ‘Bioorthogonal Chemistry’.