Perspective

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Click Chemistry in Bioconjugation: A Precision Tool for Modern Biology

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Introduction

Bioconjugation—the covalent linking of biomolecules to other molecules, such as drugs, probes, or polymers—is a cornerstone of modern chemical biology, diagnostics, and therapeutics. Traditional bioconjugation methods often suffer from low selectivity, harsh reaction conditions, and poor yields. Click chemistry, introduced by Sharpless and colleagues, has revolutionized bioconjugation by providing rapid, efficient, and highly selective reactions under mild conditions. Its bioorthogonal nature enables precise modification of biomolecules in complex biological environments without interfering with native cellular processes [1-5].

Discussion

The defining feature of click chemistry is its simplicity and reliability. Reactions such as the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), strain-promoted azide-alkyne cycloaddition (SPAAC), and thiol-ene reactions are widely used in bioconjugation. These reactions are highly chemoselective, producing minimal by-products and proceeding efficiently at room temperature and physiological pH. The modularity of click chemistry allows diverse functional groups to be incorporated into biomolecules, enabling site-specific labeling, imaging, or therapeutic conjugation.

In drug development, click chemistry facilitates targeted drug delivery and the synthesis of antibody-drug conjugates (ADCs). By selectively attaching cytotoxic drugs to antibodies or peptides, researchers can achieve precise targeting of cancer cells while minimizing systemic toxicity. Similarly, click chemistry enables conjugation of fluorescent dyes or radiolabels to biomolecules, allowing real-time tracking of cellular processes, protein localization, or in vivo imaging.

Beyond therapeutics and imaging, click chemistry is valuable in materials science and protein engineering. PEGylation, immobilization on surfaces, and the creation of multifunctional biomaterials all benefit from the efficiency and predictability of click reactions. The bioorthogonal nature ensures that modifications occur only at intended sites, preserving the function and structure of sensitive biomolecules such as proteins, nucleic acids, and lipids.

Challenges remain, including potential cytotoxicity of copper catalysts in CuAAC, which has led to the development of copper-free alternatives like SPAAC. Advances in catalyst design, photoclick reactions, and strain-promoted ligations continue to expand the scope of click chemistry, enhancing biocompatibility and reaction versatility.

Conclusion

Click chemistry has transformed bioconjugation by offering rapid, selective, and bioorthogonal methods for modifying biomolecules. Its applications span drug development, molecular imaging, protein engineering, and biomaterials, enabling precise and functional molecular modifications in complex biological systems. With

continued innovation in catalyst design and reaction strategies, click chemistry remains a cornerstone of chemical biology, bridging chemistry and biology to advance diagnostics, therapeutics, and research in a controlled and efficient manner.

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