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Opinion

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Bioorthogonal Click Chemistry for Imaging and Targeted Drug Delivery

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DESCRIPTION

Bioorthogonal click chemistry has revolutionized the fields of imaging and targeted drug delivery by providing highly selective and efficient chemical reactions that occur within complex biological systems. Bioorthogonal click chemistry refers to chemical reactions that are selective, rapid, and biocompatible, occurring selectively within biological environments without interfering with native biochemical processes. These reactions typically involve small, non-toxic reagents and proceed under mild physiological conditions, such as neutral pH and ambient temperature. The most widely used bioorthogonal click reactions include the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC), Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC), and Inverse-Electron-Demand Diels-Alder (IEDDA) reaction between strained alkynes and tetrazines.

Bioorthogonal click chemistry enables the site-specific labeling of biomolecules, such as proteins, nucleic acids, and glycans, with fluorescent probes. This approach allows for the visualization and tracking of biomolecular interactions, cellular processes, and subcellular structures in real-time using fluorescence microscopy techniques. Bioorthogonal click chemistry is utilized to conjugate imaging probes, such as fluorophores, radiotracers, and Magnetic Resonance Imaging (MRI) contrast agents, to targeting ligands or nanoparticles for *in vivo* imaging applications. These probes enable non-invasive imaging of biological processes, disease biomarkers, and drug distribution in living organisms. Bioorthogonal click chemistry facilitates the synthesis of multimodal imaging probes that combine different imaging modalities, such as fluorescence, Positron Emission Tomography (PET), and MRI, for enhanced sensitivity and spatial resolution in imaging studies. Multimodal probes allow for complementary information and multi-scale imaging of biological systems.

Bioorthogonal click chemistry reactions are integrated into the design of clickable imaging probes, including activatable probes, smart probes, and responsive probes, which undergo chemical or environmental changes upon target binding, leading to signal amplification or modulation for improved imaging contrast and specificity. Bioorthogonal click chemistry is employed to conjugate drugs or prodrugs to targeting ligands, such as antibodies, peptides, or aptamers, for site-specific drug delivery to diseased tissues or cells. These drug conjugates enhance drug efficacy, reduce off-target effects, and overcome multidrug resistance in cancer therapy and other diseases. Bioorthogonal click chemistry is utilized to functionalize nanoparticles, such as liposomes, micelles, and polymeric nanoparticles, with targeting ligands, imaging agents, and therapeutic payloads for enhanced drug delivery and controlled release at the desired site of action.

Bioorthogonal click chemistry enables the development of click-to-release prodrugs, where the drug is linked to an inactive precursor *via* a bioorthogonal linker. Upon selective activation by a bioorthogonal reaction at the target site, the prodrug is cleaved, releasing the active drug molecule, thereby minimizing systemic toxicity and maximizing therapeutic efficacy. Bioorthogonal click chemistry reactions are integrated into stimuli-responsive drug delivery systems that undergo triggered drug release in response to specific biological or environmental stimuli, such as pH, temperature, enzymes, or light, at the target site, allowing for spatiotemporal control over drug release kinetics. Bioorthogonal click reactions are orthogonal to endogenous biological processes, meaning they do not interfere with native biochemical pathways or biomolecular interactions. This orthogonality allows for the selective modification or manipulation of specific biomolecules or cellular processes without perturbing the overall cellular function. Bioorthogonal click chemistry facilitates the synthesis of multimodal imaging probes by conjugating multiple imaging modalities, such as fluorescence, PET, and MRI, to a single targeting moiety or nanoparticle.

In conclusion, Bioorthogonal click chemistry has emerged as a versatile tool for imaging and targeted drug delivery applications, offering selective and efficient chemical reactions within complex biological systems. By harnessing the principles of bioorthogonality, chemists can design and synthesize imaging probes, drug conjugates, and nanoparticle delivery systems with enhanced specificity, sensitivity, and therapeutic efficacy. Continued advancements in bioorthogonal click chemistry, coupled with innovations in imaging modalities, drug discovery, and nanotechnology, hold promise for addressing current and future challenges in biomedical research and clinical translation.