Pharaonic Journal of Science
https://pjscience.org/
PJS
SPBH

Review Article

Synthetic Organelles: Programmable Bio-Organic Compartments for Next-Generation Biocatalysis and Therapeutics

Muna S. Al-Dulaimi[1], Zubaida Khaddar Elias[2], Tamara Sh. Abdulrahman[3], and Shakir M. Saied[4]

[1] Forensic Evidence Department, College of Science, University of Mosul. Mosul, Iraq

[2]Department of Laser Spectroscopy, Laser and Photonics Center, University of AL-Hamdaniya, Mosul, Iraq.

[3]Northern Technical University, Mosul, Iraq, Email: tamara.sh.770@ntu.edu.iq

[4]College of Pharmacy, Alnoor University, Mosul, Iraq, Email: shakir.mahmood@alnoor.edu.iq

DOI: https://doi.org/10.71428/PJS.2026.0210

Abstract:

This paper reviews the development of "artificial organelles" from a simple imitation based on fat to an advanced one, "programmable" intracellular compartments planned for innovative "biomedical" applications. The field made with the development of "liposomes", which served as "foundational models" for cellular membranes and grew into effective drug transport systems like "doxorubicin HCl liposome injection" (Doxil®).

An important advancement was the overview of "polymersomes", a block copolymer are the main component of the synthetic vesicles, which proposed higher stability, tunability, and scrupulous penetrability compared to their lipid counterparts. The merging of "materials" science and synthetic "biology" then permitted a crucial shift in concentration from passive delivery of medications to active "synthetic organelles" skilled for performing complex, "multi-enzyme" cascade reactions. Encouraged by "biological" spectacles such as liquid-liquid phase separation, "membrane-free coacervates" appeared as an alternative outline for producing dynamic, organelle-like structures that can selectively confiscate biomolecules.

A serious innovation for confirming seamless integration with instinctive cellular processes is intracellular assembly using "bio-orthogonal" chemistry. Methods such as the "azide-alkyne cycloaddition using copper-catalyst" click reaction permit the exact construction of "functional materials" corresponding to hydrogels or nanostructures—in a straight line within the living cell from small, inert "precursors" that bypass delivery barriers. These progressions exposed new frontiers in biomedicine and biotechnology. In beleaguered therapeutics, they enable novel strategies such as troublesome cancer cell mechanics from within, while in "biocatalysis", they pave the way for generating self-contained metabolic factories inside cells to produce "high-value" compounds. This progression marks a move towards engineering customizable micro-factories within "living" systems.

Keywords: Click reactions, Intracellular assembly, Liposomes, Polymersomes, Synthetic biology, Synthetic organelles.

Received: March 9, 2026. Accepted: May 10, 2026. Published: June 21, 2026

Introduction:

Synthetic organelles represent an exciting horizon in the field of modern bioengineering, as they emerge from deep contemplations of cell biology and are propelled forward thanks to advances in nanotechnology, polymer science, and synthetic biology. This narrative embodies humanity's effort to mimic one of nature's most complex designs, "cellular compartmentalization," in order to engineer specialized micro-factories and functional agents within living systems [١].

The finding of the "eukaryotic" cell laid the historical basis for understanding a significantly more complex level of "biological" organization. Also, eukaryotic cells are "meaningfully more complex than prokaryotic cells," a representative defined by their high grade of internal organization. This complexity contains a "membrane-enclosed" nucleus housing the cell's DNA, along with numerous specialized organelles such as mitochondria, the endoplasmic reticulum, and the Golgi apparatus, each performing specific and vital functions [2].

The discovery of the "eukaryotic" cell, fig. 1, laid the historical basis for understanding an additional and significantly more complex level of "biological" organization. Also, eukaryotic cells are "significantly more complex than prokaryotic cells," and representatives have defined them as having a high degree of internal organization. This complexity includes a "membrane-enclosed" nucleus that contains cell DNA, along with several specialized organelles such as mitochondria, endoplasmic reticulum, and the Golgi apparatus, each of which performs specific and vital functions [2].

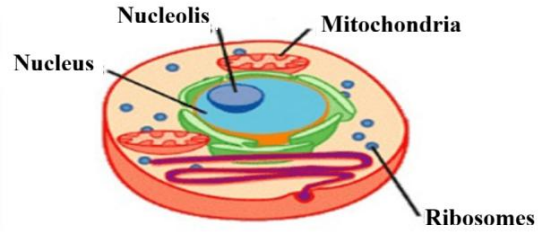


fig. (1):
The eukaryotic cell, [] [3]

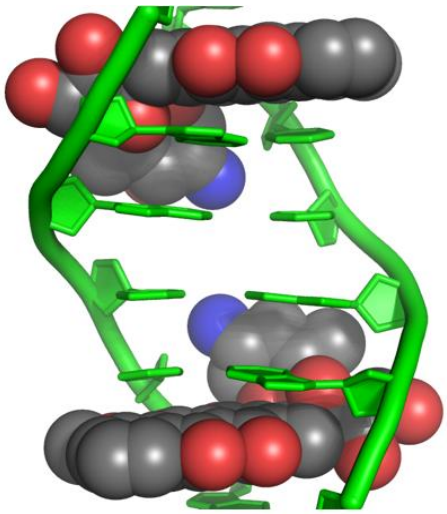
All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

The scientists have predictable that “membrane-bound compartments” alike the nucleus, “mitochondria”, and endoplasmic reticulum are not just anatomical features, but they are vital for life's complexity, permitting the cell to insulate incompatible reactions and avoid enzymes especially the digestive in the lysosome from corrupting the entire cell, this concentrate reactants increase the local concentration of substrates and enzymes to increase biochemical “efficiency” and create unique microenvironments, sustain specific ion concentrations, pH or redox potentials [4].

At the end of the last century, the pre-synthesis phase was characterized by simple simulations, the initial phase was about simulating the organisms found in the laboratory, and the main revolution was the development of "leptosomes by Alec Bingham", as these simple lipid bimembranes, which self-assemble to form vesicles, provided the first concrete model of a cell membrane. Alec Bingham discovered that lipids could form small "bubbles" called leptosomes, and this provided scientists with a simple model for studying the cell membrane, which later evolved into an important biotechnology to deliver targeted medicines and vaccines, saving millions of lives [5].

The new applications were started at the end of the last century, specifically between the years 1980 and 1990. encapsulating the enzymes and medication within “liposomes”. placed the groundwork for the first FDA-approved liposomal drug delivery, the doxorubicin HCl liposome injection, which is an antineoplastic medication (Doxil®), which it is clinically used with notable applications in ovarian cancer, multiple myeloma, and AIDS-related Kaposi's sarcoma[6].

This drug works by stabilizing the topoisomerase II enzyme after it breaks the DNA strand by its two molecules which intercalating DNA, from, this action traps the DNA in a broken state, preventing the double helix from resealing and ultimately halting the process of replication, an additional effect involves the generation of quinone-like free radicals, which is thought to contribute to the drug's cell-killing ability, figure (2) [7].



[8]

Fig. (2): Diagram of the two Doxil molecules intercalating DNA

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

At the end of the twentieth century, a paradigm shift in biotechnology, from simply using vesicles as carriers to engineering them as functional incubators. This shift was driven by the intersection of materials science and "bioengineering" [9].

A major advance was the introduction of polymers—vesicles made of synthetic "mass copolymers" that offered a more robust and tunable alternative to traditional liposomes, and these advances allowed engineers to propose polymers with precise properties, such as micro-permeability, high stability, and synthetic biodegradability customized [10].

At the same time, advances in synthetic biology made it possible to create standardized biological fragments, such as "catalysts, genes, and proteins," allowing for the engineering of new functions and metabolic pathways within these vesicles. This was enhanced by nanobiotechnology, which introduced the idea of "smart" materials. These materials could be mapped to respond to specific stimuli such as molecular signals, "pH," heat, or light, and were incorporated into the design of the vesicles to create "dynamically responsive systems" [11].

During the period from the late 2000s to the early 2000s, the term "prosthetic organelle" began to emerge. The "goal" was no longer just to connect, but to create a compartment that could achieve a catalytic function within the cell [12].

Preliminary demonstration studies focused on multi-enzyme pathways within the vesicles to achieve cascading reactions, fig 3, and the design of pore-walled membranes that can allow substrates to enter and exit products selectively, [13,14].

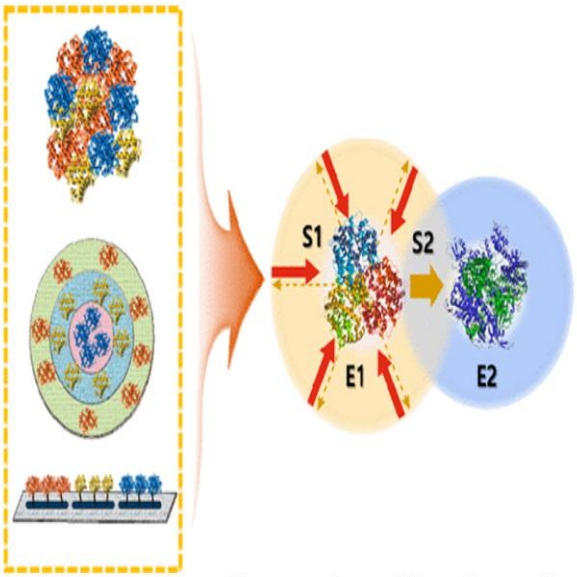


Fig. (3): The encapsulating multi-enzyme pathways within vesicles to perform cascading reactions,[Hwang and Seonbyul, (2019)] [15]

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

Multienzyme chain reactions are crucial for efficient synthesis in pharmaceuticals, cosmetics, and nutrition. A key strategy for developing these reactions is to assemble enzyme complexes across three main methods:

a. Fusion proteins
b. Enzyme scaffolds
c. Immobilization.

New progress in materials science has prolonged the options for immobilization, with methods including arbitrary "co-immobilization, compartmentalization, and positional co-immobilization". These structured multienzyme systems offer significant advantages, primarily by enabling substrate channeling to enhance reaction efficiency, alongside improved enzyme stability and the practicality of catalyst recovery and reuse, fig. 3 [15].

Scientists reentered an old "hypothesis about the beginning" of life of those simple compartments formed through liquid-liquid phase parting "coacervates", these membrane-free condensates, like the "nucleolus" in up-to-date cells, offered a new "blueprint" for creating organelle-like structures that could selectively "confiscate biomolecules" with high efficiency, fig(4),[16].

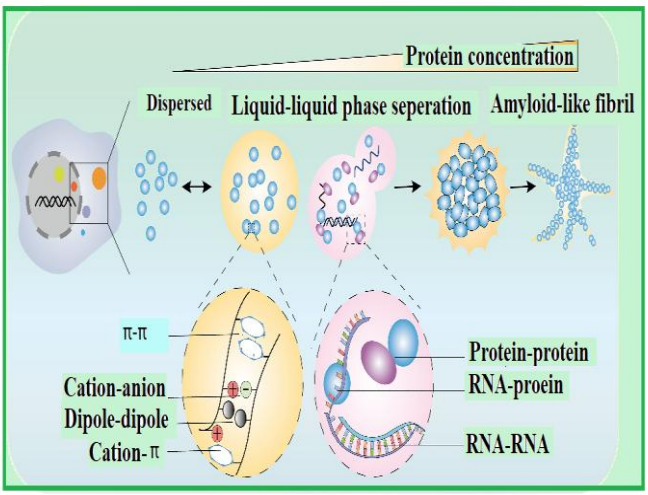


fig. (4): Liquid-liquid phase separation (Coacervates)[Shin and Brangwynne, (2017)] [16]

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

The major challenge in this field was 'engineering synthetic organelles' to seamlessly integrate with the host cell's metabolism. To address this, researchers created systems capable of detecting signals within the cell such as reactive oxygen species (ROS) or ATP levels, and responding by releasing a therapeutic payload or activating a specific enzyme. Moving beyond the injection of pre-formed vesicles, scientists have pioneered targeted intracellular assembly approaches. These methods trigger the self-assembly of synthetic organelles inside living cells. This is realized either by using genetically encoded tags to recruit engineered protein components to specific locations (e.g., the centrosome) or by employing bio-orthogonal chemistry to initiate assembly from small molecules that diffuse into the cell [17]

Now, what is bio-orthogonal chemistry?

The major challenge in this field was the 'engineering of synthetic organelles' to integrate seamlessly into the host cell's metabolism. To address this, researchers created systems capable of

detecting signals within the cell, such as reactive oxygen species (ROS) or ATP levels, and responding by releasing a therapeutic payload or activating a specific enzyme. This triggered interaction initiates the "self-assembly" of the precursors into a greater, functional structure, such as a "nanostructure, hydrogel, or scaffold" directly within the intracellular environment. This approach elegantly disables the fundamental challenge of delivering pre-formed macromolecules into cells, enabling the building of complex architectures in situ [18]. The primary objective is to create these functional materials from within, after the building blocks have safely entered the cell.

This technique can be applied by engineering two or more small molecules, each bearing a biologically orthogonal chemical "handle" like the widely used alkyne-azide cycloaddition reaction. These molecules are planned so that upon encountering each other inside the cell, their complementary handles engage in a rapid and irreversible reaction, triggering the assembly process. Thus, using dibenzocyclooctyne (DBCO) reagent, fig (5), which is a class of click chemistry labeling reagents (the chemical concept that won the Nobel Prize in Chemistry in 2022 for scientists Caroline Bertuzzi, Morten Mildahl, and Barry Sharpless with the goal that is to bind two different molecules together easily and reliably, as a safety belt attaches. The reaction should be fast and effective, and occur even at low concentrations. It selectively reacts only with its specific chemical groups without affecting any other part of the molecule, and it is also compatible with water and can be performed in physiological conditions (e.g., intracellular) [19].

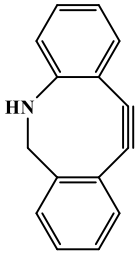


fig. (5): The chemical structure of dibenzocyclooctyne (DBCO) reagent

All chemical structures in this paper figures were drawn using ChemDraw® Professional,

The dibenzocyclooctyne (DBCO)-based click chemistry labeling reagent is engineered to undergo copper-catalyzed azide–alkyne cycloaddition (CuAAC) with azide-functionalized molecules or biomolecules. This bioorthogonal reaction forms a stable 1,2,3-triazole linkage, enabling the site-specific attachment of a fluorescent label to newly synthesized proteins within living cells. Cells are fed an azide-containing analog that mimics a natural amino acid; the cellular machinery incorporates this analog into nascent proteins during translation. Subsequent addition of the DBCO–fluorophore conjugate triggers a rapid and selective click reaction, covalently labeling the azide-tagged proteins. When multiple labeled proteins interact through their conjugated fluorophores or cross-linking moieties, they can form a dense, gel-like polymeric network in the cytoplasm. This intracellular matrix alters the physical properties of the cell, transforming the cytosol from a viscous fluid into a more rigid gel—thereby restricting cellular motility and impairing critical functions, particularly in cancer cells [20,21].

Organic Chemistry:

The protocol for the synthesis of the regioisomeric five-membered heterocyclic compounds of three nitrogen atoms (triazoles) under thermal conditions and with copper (1) species catalyst following 1,3-dipolar cycloadditions of organic azides and acetylenes (alkynes) is afforded high yield and short time rate, fig. (6) [22,23].

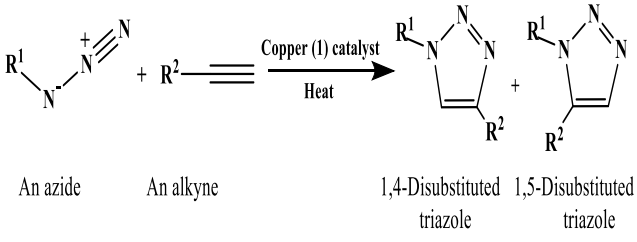


fig.(6) : The general reaction of the disubstituted triazole isomers

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

Why is the 1,3-dipolar cycloaddition between organic azide and alkyne referred to as such?

This is because the addition of the acetylide ion (derived from a terminal alkyne) to the azide ion occurs at terminal nitrogen number 1 of the azide (which is the most electrophilic). Meanwhile, the nucleophilic nitrogen atom number 3 of the azide ion attacks the partial positive carbon atom of the acetylide ion, fig.(7), [24].

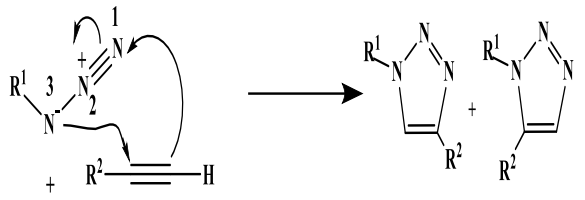


fig. (7): Why does the 1,3-dipolar cycloaddition between organic azide and alkyne referred to as such? [25]

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

The coordination with copper metal enhances the nucleophilicity of the acetylide ion (derived from a terminal alkyne) by increasing the alkyne's acidity.

This reaction mechanism of using the copper-catalyzed is called the Huisgen cycloaddition reaction, of the azide-acetylene reaction (CuAAC). The acetalide ion ($^{-}C\equiv C-R$) derived from terminal alkyne is indeed a good nucleophile, but its nucleophilicity is not high enough to effectively attack the azide molecule which is considered a weak electrophile and thus here the role of copper Cu(I) is play as a copper monocatalyst (Cu(I) which coordinates with the triple bond in the terminal alkane, this coordination is like "pulling" a cloud of electrons in the triple bond towards a partially positive copper atom, this pulling of the electron cloud (through π-back bonding) inhibits (stabilizes) the resulting conjugation base after proton deduction, in other words, the resulting acetalide ion ($Cu\text{-}C\equiv C\text{-}R$) becomes more stable than the free acetalide ion, and become more acidic, i.e. it's easy to remove the proton from it. This increase in acidity turns into improved nucleophilicity, and the direct result is that the acetalide ion concentration in the reaction medium becomes much higher. In addition, the acetylide-copper complex itself is more electrophilic than the free acetylide ion, making it a stronger nucleophile when attacked by the azide molecule. The copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC) mechanism is explained in fig. (8) as shown by Bock and coworkers, [25].

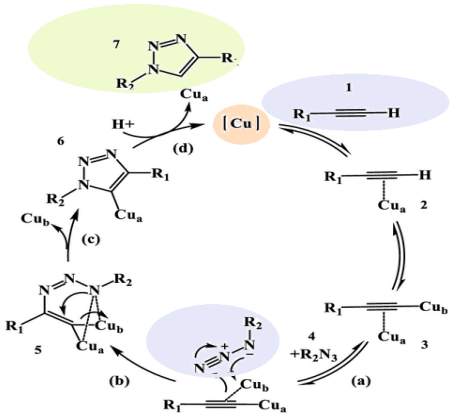


fig.(8): The CuAAC mechanism for triazole ring formation, [Bock et al., (2006)] [25]

All chemical structures in this paper figures were drawn using ChemDraw® Professional, Version 16.0 (PerkinElmer Informatics)

It is important to note that deprotonation is possible in aqueous media without the need for base, as calculations have shown that copper coordination increases the acidity of the alkyne proton by up to 9.8 pH units. The organic azide can then coordinate to a copper center in two different ways: an end-on fashion achieved by binding to the copper with the terminal nitrogen, or through the carbon-linked nitrogen. The mechanism would then proceed via a six-membered metallacycle transition state to the copper triazolide species, which would undergo reductive elimination to furnish the 1,4-disubstituted triazole and close the catalytic cycle.

The revolutionary potential of intracellular hydrogelation lies in its ability to engineer the cellular environment from within. This technique

enables the creation of an artificial "skeleton" inside the cell, altering its mechanical properties to potentially inhibit cancerous transformation. Furthermore, these systems can be designed to entrap therapeutic agents, releasing a drug with extreme precision only after the hydrogel assembly is triggered. This paves the way for bestowing novel functions upon cells, such as the introduction of unnatural enzymes to produce pharmaceutical compounds, thereby creating cellular factories. For fundamental research, it provides an unparalleled tool for scientists to observe and manipulate biological processes with high spatiotemporal control, offering a dynamic window into cell biology [26,27].

Acknowledgement:

The author would like to express sincere gratitude to Al-Noor University for generous financial support (ANUI/2025/SCI22). The university's proactive policy of encouraging research and rewarding scholarly publishing is highly commendable.

Conflict of interest: NIL

Funding: NIL

References:

1. Fabrini G, Farag N, Nuccio SP, Li S, Stewart JM, Tang AA, McCoy R, Owens RM, Rothemund PW, Franco E, Di Antonio M. Co-transcriptional production of programmable RNA condensates and synthetic organelles. Nature Nanotechnology. 2024 Nov;19(11):1665-73.
2. Vanhov S, Bosc C, Couté Y, Crispi S, El Khoury V, Gérard D, Hervouet E, Lomonte P, Pezet M, Valton A. The expanding family of histone variants: A complex toolbox for fine-tuning chromatin organization. Biol Cell. 2022;114(11):289-304.
3. wang L,chen y,patel R,johson T,Ahmed S,zhao H ,kumar P .Advances in imaging and functional analysis of eukaryotic cell organelles.Not Rev Mol Cell Bio .2025Feb;26(2):145.162.
4. Alberts B, Heald R, Johnson A, Morgan D, Raff M, Roberts K. Molecular biology of the cell. 7th ed. New York: W.W. Norton & Company; 2022. p. 695-723.
5. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. Front Pharmacol. 2015;6:286.
6. Sun Pharmaceutical Industries Inc. Doxorubicin HCl liposome injection [Prescribing Information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; 2023.
7. Zhang Y, Moralis A, Singh R, Chen J, Gupta N, Li W.Structural insights into anthracyclin –DNA intercalation and its implications for cancer therapy.j med chem .2024 Nov;67(21):14532-14545
8. Tacar O, Sriamornsak P, Dass CR. Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. J Pharm Pharmacol. 2013;65(2):157–170.
9. Zhou X, Huang Q, Yang YJ, Tang H, Zhang L, Li D, Xu Y. Emerging technologies for engineering of extracellular vesicles. *Front Bioeng Biotechnol.* 2023 Nov 8;11:1298746. doi:10.3389/fbioe.2023.1298746.
10. Liu L, He H, Zhang J. Advances in polymersomes for biomedicine. Pharmaceutics. 2021;13(6):879.
11. Gopfrich K, Platzman I, Spatz JP. Mastering complexity: towards bottom-up construction of multifunctional eukaryotic synthetic cells. Trends Biotechnol. 2018;36(9):938–951.
12. Peters RJ P, Marguet M, Marais S, Fraaije MW, van Hest JCM, Lecommandoux S. Cascade reactions in multicompartmentalized

polymersomes. Angew. Chem. Int Ed Engl. 2014;53(1):146–150.

13. Mason AF, Buddingh' BC, Williams DS, van Hest JCM. Hierarchical self-assembly of a copolymer-stabilized coacervate protocell. J Am Chem Soc. 2017;139(48):17309–17312.
14. Liu X, Zhou P, Huang Y, Li M, Li F, Li D. Construction of artificial organelles based on giant unilamellar vesicles. Chem Soc Rev. 2022;51(19):8311–8333.
15. Hwang ET, Seonbyul L. Multienzymatic cascade reactions via enzyme complex by immobilization. ACS Catal. 2019;9(5):4402–4425. doi: 10.1021/acscatal.9b00225
16. Shin Y, Brangwynne CP. Liquid phase condensation in cell physiology and disease. Science. 2017;357(6357):eaaf4382.
17. Lee D, Lim Y, Lee S, Ryu J, Oh Y. Co-assembly of synthetic organelles with spatially selective cargo. Nat Commun. 2023;14(1):4862. doi: 10.1038/s41467-023-40410-x
18. Zhou J, Li Y, Du X, Xu B. Intracellular construction of supramolecular nanostructures for biomedical applications. Chem Soc Rev. 2022;51(15):6333–6350.
19. Peng Y, Thery F. Spatiotemporal control of biomolecular condensates and their functions. Curr Opin Chem Biol. 2023;74:102305. doi: 10.1016/j.cbpa.2023.102305
20. Sletten EM, Bertozzi CR. Bioorthogonal chemistry: fishing for selectivity in a sea of functionality. Angew Chem Int Ed. Engl. 2009;48(38):6974–6998. doi: 10.1002/anie.200900942
21. McKay CS, Finn MG. Click chemistry in complex mixtures: bioorthogonal bioconjugation. Chem Biol. 2014;21(9):1075–1101. doi: 10.1016/j.chembiol.2014.09.001
22. Tornøe CW, Christensen C, Meldal M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. J Org Chem. 2002;67(9):3057–3064. doi: 10.1021/jo011148j
23. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. Angew Chem Int Ed. Engl. 2002;41(14):2596–2599.
24. Hein JE, Fokin VV. Copper-catalyzed azide–alkyne cycloaddition (CuAAC) and beyond: a reactivity landscape. Chem Soc Rev. 2021;50(8):4804–4811.
25. Bock VD, Hiemstra H, Van Maarseveen JH. Cu I-catalyzed alkyne-azide "click" cycloadditions from a mechanistic and synthetic perspective. Eur J Org Chem. 2006;2006(1):51–68. doi: 10.1002/ejoc.200500483.
26. Chen TJ, Reynolds DS, Goulbourne E, Zhang LF, Hu YJ, Xue SH. Programmable assembly of a metabolic hydroscaffold for sustained drug release and modulation of tumor microenvironment. Nat Biotechnol. 2023;41(8):1122–1130.
27. Santos HA, Li J, Del Valle AC, Wang Y, Kroll AV, Luo D. In situ synthesis of artificial organelles via bioorthogonal nanogel condensation for enhanced enzyme cascades. Science. 2022;378(6625):1065–1071.