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Biomedicine COMMENTARY

MOFs: From programmable porous crystals to precision biomedicine

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Received: October 20, 2025; Accepted: March 30, 2026; Published Online: April 2, 2026; https://doi.org/10.59717/j.xinn-life.2026.100211

Citation: Zhao Y., Chu P. and Wang H. (2026). MOFs: From programmable porous crystals to precision biomedicine. *The Innovation Life* **4**:100211.

The 2025 Nobel Prize in Chemistry was awarded to Susumu Kitagawa, Richard Robson, and Omar M. Yaghi for their development of metal-organic frameworks (MOFs). Professor Heiner Link, the chair of the Nobel Committee for Chemistry, remarked in the award speech: MOFs can be created with unlimited variations unending possibilities for the greatest benefit to humankind. Their customizable nature allows scientists to design molecular-scale "rooms" like architects, thereby addressing global challenges such as those in energy and the environment. This hints at a deeper underlying logic behind the award: the award may not be solely for MOFs as a material, but rather the paradigm shift in materials from synthesis to programming. It signifies the precise programming and customization of material structure and function at the molecular level.

MOFs have shown promise in translational research, as evidenced by the first clinical trial of a MOF-based radioenhancer RiMO-301 for solid tumors

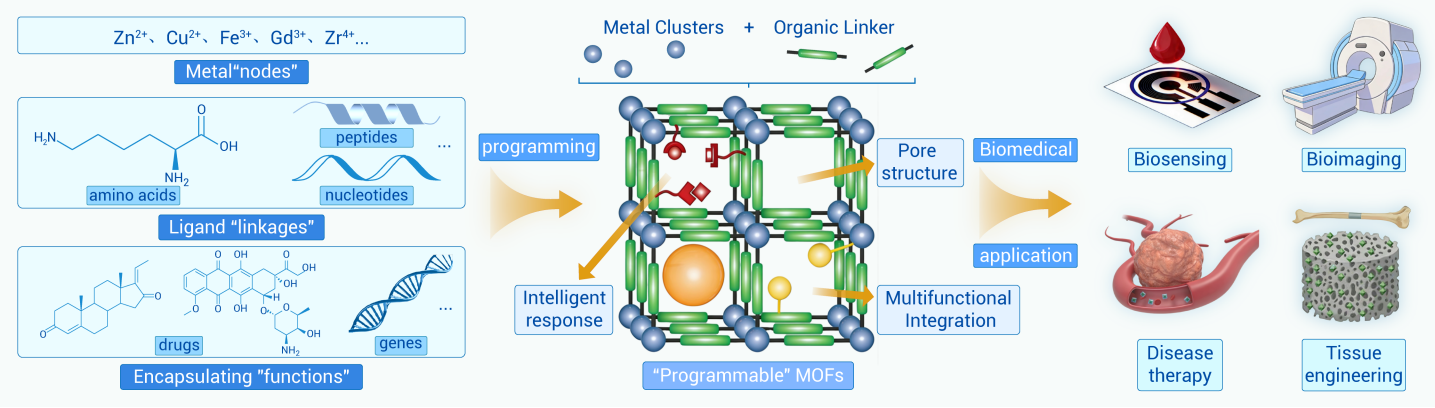

Figure 1. Programmability and application of MOFs.

(NCT05838729) and RiMO-401 (NCT06182579) for advanced tumors in combination with radiation therapy. The programmability of MOFs has been demonstrated in biomedicine and allows researchers to precisely code the composites (cations and ligands), physicochemical properties (pore, topology, and default), and biological application (sensing, imaging, and therapeutics). Comparing with other nanomaterials such as mesoporous silica and polymeric nanoparticles, the advantage of MOFs lies in their unparalleled programmability and unity of structure and function. It is not only a passive carrier, but also a platform that integrate abundant chemical reactivity and intrinsic functions.

Using biocompatible metal nodes such as zirconium, iron, zinc, gadolinium, copper, etc. as nodes and organic ligands like carboxylic acids, amino acids, nucleotide derivatives, peptides, etc. as functional linkage, MOFs can be constructed by selecting different combinations. This provides a programming property for materials development:

(1) Defining Variables (Pore Structure): By adjusting the length and angle of ligands, the size and shape of pores can be defined, akin to customizing exclusive rooms for specific molecules. (2) Writing Conditional Statements (Intelligent Response): By incorporating groups sensitive to specific stimuli such as pH, light, enzymes, etc. conditional logic can be programed for MOFs: IF (environmental pH < 6.5) {THEN (structure collapses, releasing drugs)}, or IF (exposed to near-infrared light) {THEN (generate heat or reactive oxygen species)}. (3) Encapsulating Functions: The pores act like a function library, capable of encapsulating multiple functions within a single particle. This programmability transforms MOFs from mere static objects into agents that can dynamically respond to complex signals in living organisms. Their applications in biosensing, bioimaging, and critical therapeutic areas make MOFs promising platform for precision medicine (Figure 1).

In the field of biosensing, the large specific surface area and functional pores of MOFs render them possibility to capture target molecules and generate specific signal responses, such as fluorescence, electrochemical, electrochemiluminescence, and colorimetric signals. Thin-film sensors developed based on MOFs enable rapid and sensitive disease screening by selectively adsorbing specific volatile organic compounds (VOCs).[1] Furthermore, designing MOF probes that are sensitive to specific physiological parameters (such as pH, reactive oxygen species, glutathione, or enzymes) enables discrimination between cancer cells and normal cells. Logic gate-based MOF biosensors, which integrate Boolean logic operations (AND, OR, NOT) with sensing mechanisms, have also shown promising potential in sensor applications.

In bioimaging, MOFs significantly enhance the performance. In magnetic resonance imaging, incorporating gadolinium (Gd^{3+}) ions as nodes into the MOF network creates a synergistic effect due to their periodic arrangement to substantially improve the imaging efficacy.[2] When heavy metal ions are incorporated into the pores, MOFs serve as effective contrast agents for CT imaging. As optical imaging agents, MOFs can enhance or modulate fluorescence signals by adjusting their internal pore structures and performing surface modifications, consequently enabling high-resolution fluorescence imaging.

In the field of disease therapy, MOFs can be programmed to control drug delivery and release strategies to realize precise therapy for enhanced therapeutic efficacy and reduced side. Early MOFs function as intelligent containers to enable targeted release of chemotherapy drugs in the tumor microenvironment. Different drug release behaviors can be programmed into MOF particles in response to endogenous stimuli, such as pH, enzymes, GSH, H_2O_2, H_2S, ATP, etc., or external stimuli like magnetism, temperature, pressure, light and Boolean logic gate-based stimuli. Advanced tumor therapy enables the co-loading of chemotherapy drugs with other therapeutic agents, such as photosensitizers, immune agonists, etc. within a single MOF, allowing combined tumor therapies to synergistically treat tumors while preventing recurrence and metastasis.[3]

In tissue engineering, MOFs serve as programmable scaffolds, issuing

precise instructions to cells. For instance, in neural repair, MOFs can be programmed to design bioadaptive neural interfaces, improving oxidative metabolism in damaged nerves and reshaping the neural microenvironment to promote nerve regeneration.[4] In bone repair, specifically programmed MOFs can simultaneously achieve pH neutralization, enhance osteogenic differentiation and inhibit osteoclast activity. Additionally, MOFs programmed with diverse cargoes like biomolecules, antibiotics, and antioxidants can facilitate skin wound healing by orchestrating multiple therapeutic effects. In cardiovascular engineering, the effectiveness of MOFs-based materials has been validated in atherosclerosis, thrombosis, myocardial infarction, critical limb ischemia, and vascular implants.[5]

The Nobel Prize is certain to further accelerate MOFs research in biomedicine, but the path to clinical application remains fraught with challenges. The first hurdle lies in the toxicity and biosafety. A set of intrinsic factors-including chemical composition, dose, size, shape, and surface chemistry-collectively dictates the biological behavior and therapeutic performance of MOFs. Importantly, these very same properties also underlie their potential for long-term toxicity, primarily by triggering adverse mechanisms such as reactive oxygen species production, cell membrane disturbance, hemolysis, or complement system interactions. Programming the MOFs on those factors to avoid off-target effects and unintended toxicity represents the ultimate test before they can be approved for clinical use.

The stability and controlled biodegradation of MOFs in biological environments remain another challenge. As their structure is held by coordination bonds, factors including local pH, salt concentration, and the intracellular compartments can trigger degradation *via* mechanisms like proton-assisted hydrolysis, ligand exchange or enzymatic degradation. This decomposition directly impacts the MOFs' biological fate and toxicity profile. The coordination stability of MOFs, governed by the nature of the metal and linker, can be programmed according to the hard and soft acids and bases (HSAB) principle, and further enhanced through surface modification (e.g., PEGylation) or drug incorporation.

The third challenge comes from mass production. Conventional solvothermal synthesis is the mostly employed method to obtain MOFs, but it is difficult to guarantee the crystallinity and consistency when the synthesis is scaled up. Transforming exquisitely controlled gram-scale synthesis in the laboratory into kilogram-scale, batch-stable drug production serves as the cornerstone for ensuring its safety and efficacy. On the other hand, the precise control of structural properties-such as pore size, ligand orientation, and defect density-is equally critical. An efficient means of regulating morphology and size is the use of modulators, including inorganic/organic bases and monocarboxylic acids, which alter acid-base equilibria in the reaction system or compete with organic linkers. Alternatively, templating strategies provide another powerful approach to direct MOF topology and porosity. The introduction of template molecules, ranging from small organics and coordination compounds to polyoxometalates and biomacromolecules, enables engineering of pore channel systems.

Finally, there are challenges in the optimization of programming. The current understanding of the "structure-property" relationship is still at a rudimentary level. In the future, leveraging artificial intelligence (AI) and high-throughput will be essential to achieving reverse automated design from desired functions to molecular structures. By previously defining performance objectives and leveraging suitable secondary building units optimized *via* machine learning or heuristic algorithms, the inverse design strategy enables more accurate material discovery of MOFs.

The 2025 Nobel Prize in Chemistry honors not merely a material, but the dawn of an era of programmable matter. MOFs have demonstrated that biomaterials of the future will be intelligent systems, designed based on profound scientific principles, capable of processing information and executing tasks. From sensing logic to therapeutic strategies, and even regenerative instructions, MOFs act as a universal translator between biology and materials science, enabling us to use the language of chemistry to write precise scripts for the repair and regeneration of life.

REFERENCES

1. Jin K., Moon D., Chen Y.-P., et al. (2024). Comprehensive qualitative and quantitative colorimetric sensing of volatile organic compounds using monolayered metal-organic framework films. *Adv. Mater.* **36**:2309570. DOI:10.1002/adma.202309570
2. Zhang S.-Y., Wang Z.-Y., Gao J., et al. (2019). A gadolinium (III) zeolite-like metal-organic-framework-based magnetic resonance thermometer. *Chem* **5**:1609–1618. DOI:10.1016/j.chempr.2019.04.010
3. Shao Y., Liu B., Di Z., et al. (2020). Engineering of upconverted metal–organic frameworks for near-infrared light-triggered combinational photodynamic/chemo-/immunotherapy against hypoxic tumors. *J. Am. Chem. Soc.* **142**:3939–3946. DOI:10.1021/jacs.9b12788
4. Yao X., Yan Z., Liu A., et al. (2023). Metal organic framework-modified bioadaptable implant potentiates the reconstruction of nerve microenvironment via immunometabolism reprogramming. *Nano Today* **49**:101814. DOI:10.1016/j.nantod.2023.101814
5. Ge X., Liu Y., Zhao X, et al. (2025). Advances in metal-organic frameworks for cardiovascular therapy: From structural design to preclinical applications. *Coord. Chem. Rev.* **544**:216971. DOI:10.1016/j.ccr.2025.216971

FUNDING AND ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Grant Nos. 82350710800 and 82272157), Shenzhen Science and Technology Research Funding (Grant No. JCYJ20241202125205007), City University of Hong Kong Donation Research Grants (DON- RMG 9229021 and 9220061), and Guangdong - Hong Kong Technology Cooperation Funding Scheme (TCFS GHP/212/22GD and CityU 9440399). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Yuetao Zhao and Huaiyu Wang conceived the idea. Yuetao Zhao prepared the manuscript. Paul K. Chu and Huaiyu Wang revised the manuscript. All the authors have approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.