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Tailorable fabrication of optical active nanomaterials for bio-applications

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Abstract: The unique properties of nanoscale materials exhibiting chirality, such as their catalytic, optical and photothermal capabilities, have been recognized for their exceptional potential in bio-applications. The optical active nanomaterials have attracted significant attention due to their valuable contributions to the fields of biocatalysis, biosensing and nanomedicine, marking a period of notable progress and innovation. In this review, we delve into the most recent advancements in this rapidly evolving field, aiming to provide a thorough insight into the progress made with optically active nanomaterials and to inspire further advancements in bio-applications.

Keywords: bionic synthesis; biocatalysis; biosensing; nanomedicine

1. Introduction

Over the past few years, inorganic nanoscale entities have demonstrated the capacity to modulate chiral optical signals within the visible and near-infrared spectrum, thereby amplifying optical responses. This is attributed to their high polarizability and tunable optical properties based on their shape. However, these inorganic nanomaterials often fall short in terms of target specificity and can exhibit considerable toxicity when introduced into biological systems [1,2]. The integration of chiral biomolecules with inorganic nanomaterials presents a promising solution for challenges. These biomolecule-guided chiral nanostructures not only exhibit a high degree of specificity in target recognition but also possess minimal biological toxicity. Moreover, they allow for the modulation of optical activity through the regulation,

assembly and induction of inorganic nanomaterials. As a result, biomolecule-mediated chiral nanostructures have garnered extensive interest across various fields, including the synthesis of chiral biomimetic materials, biocatalytic processes, biosensing and nanomedicine [3].

However, the distribution, metabolism and potential toxicity of optical active nanomaterials within biological organisms still require in-depth investigation. Furthermore, researchers need to gain a deep understanding of the underlying mechanisms of the interaction between chiral nanomaterials and biological cells to optimize their application in biomedicine. This perspective aims at providing an exhaustive review of the synthesis, applications and existing challenges associated with optical active nanomaterials for bio-applications. It also aims to inspire further advancements in bio-applications.

2. Bionic synthesis

The chiral properties of nanomaterials are significantly enhanced through the incorporation of biomolecular modifications, including nucleic acids, peptides, proteins and polysaccharides, which contribute an additional layer of chirality beyond the inherent characteristics of artificial macromolecules. Artificial nanoparticles with a precise chiral structure present a great challenge, both in design and synthesize in advance [1–3]. Chiral ligands can be integrated at various stages of nanoparticle synthesis—initially, midway or post-synthesis—to mediate their construction. Initially, these ligands and metal ions form complexes, leading the formation of inorganic cores. The presence of chiral ligands can induce distortion of the crystal lattice, therefore, the chiral optical activity of inorganic nanoparticles is enhanced. The synthesis of chiral nanomaterials typically involves a multi-step process, gold nanocubes with high Miller index facets are first created as seed particles. Subsequently, chiral organic ligands like glutathione or cysteine are modified to these facets to direct the regrowth phase, yielding nanomaterials with pronounced chiral optical activity. Furthermore, helical nucleic acids can be assembled into super-helical structures under the influence of high concentration chiral ligands and transferring their chirality to otherwise achiral azo-benzenes as well [4–6]. Beyond these methods, post-translational modifications of synthesized nanoparticles offer another way for the creation of chiral nanomaterials. In addition, the self-assembly of nanomaterials facilitated by precise geometric control at the nanoscale has found broad applications in biosensing, chiral catalysis and photonics (Figure 1 Bionic synthesis). Biomolecules, characterized by their charged surfaces maintain their helical structures at a neutral pH. Amino groups in peptides confer a positive charge, while carboxyl groups in DNA and some peptides result in a negative charge. The propensity for hydrogen bonding in these molecules is substantial, enabling the use of non-covalent intermolecular interactions such as hydrogen bonding, electrostatic forces, coordination and hydrophobic interactions in self-assembly processes. The chiral nanomaterials produced according to these different synthesis methods have different properties (Table 1) [7–10].

Table 1. Synthesis methods, chirality origin and properties of chiral nanomaterials.

S No	Synthetic method	Chirality origin	Properties	References
1	Chiral ligand-mediated construction method	Ligand induced chirality	Unique morphologies and specific functions.	[7]
2	Nanoparticle interaction facilitated assembly	Chiral superstructure	Chiral light-matter interactions	[4]
3	Chiral external field induced assembly		Well-defined helicity	[6]
4	Chiral template induced assembly		Strong interparticle contacts and well-defined helicity	[5]

However, the way towards the practical application of optical active nanomaterials is still in its early stages. To broaden the applicability of biomolecules and refine their optical properties, there is an urgent need to investigate a wider range of amino acids, peptides and proteins as potential chiral ligands, beyond those containing thiol groups. It is also imperative to gain a comprehensive understanding of the mechanisms behind the formation of chiral nanostructures and study the integration of chiral organic ligands with other materials to produce robust circular dichroism (CD) signals. Mathematical structure, pattern analysis and computational modelling are needed to understand chirality's role in biological assembly and function, guiding the engineering of bionic chiral particles and their targeted assembly.

3. Bio-applications

3.1. Biocatalysis

Optical active nanomaterials exhibit remarkable robustness and efficiency, positioning them as promising candidates for biocatalytic applications, surpassing the capabilities of conventional chiral catalysts. The development of artificial enzymes with chiral catalytic properties has been extensively pursued, owing to their remarkable efficacy in pharmaceuticals, biotransformation processes and the modulation of physiological activities [11,12]. These chiral inorganic nanomaterials are capable of emulating the catalytic functions of biological systems, offering a viable solution to the inherent defect of natural enzymes, such as economic inefficiency in extraction, diminished stability in structure and activity and the challenges posed by their reuse. The interplay between nanoparticles and chiral ligands within chiral nanomaterials is pivotal in attaining enhanced catalytic performance. The alignment of dimensions, strategic modifications and the presence of catalytically active sites are instrumental in boosting the catalytic activity and selectivity towards specific substrates. The heterogeneous nature of nanoparticle compositions contributes to the amplification of optical, electrical and magnetic properties, which in turn, can augment catalytic processes. To facilitate better separation from substrates, chiral nanostructures can be scaled up to the submicron and micron levels, as exemplified by the transition from thin nanoscale films to micron-scale solid films [13,14]. The manifestation of

optical activity, driven by the rotation of light, is advantageous for efficient catalysis. The chiral core of nanoparticles often accelerates catalytic reactions, with enantioselectivity being influenced by the interface between chiral molecules and the nanoparticle surface (Figure 1 Biocatalysis). Typically, the inorganic core provides the necessary electrons and holes to facilitate catalytic chemical reactions. Chiral nanomaterials, acting as artificial nano-enzymes, display a range of enzyme-like activities that can be modulated by adjusting their composition, structure and chiral ligands. Compared to their natural counterparts, these artificial chiral nano-enzymes not only exhibit adjustable catalytic activity but also maintain robust catalytic functions in harsh environments, such as acidic tumor microenvironments. To bolster the biocatalytic efficiency, a variety of chiral nanomaterials have been engineered, with efforts to refine their chiroptical responses by tuning the chiral organic ligands and controlling the morphology of the inorganic nanomaterials. With heightened chiral responses, these materials can harness circularly polarized light (CPL), distinguishing between left and right circular polarization, to generate a surplus of hot electrons and reactive oxygen species (ROS), which are crucial for the catalysis of biological macromolecules and *in vivo* biocatalysis [15].

Despite the significant advancements in chiral nanomaterials for catalytic applications, challenges persist. Some chiral nanomaterials still fall short in catalytic performance when compared to natural enzymes. Chiral ligands are pivotal in asymmetric catalysis, yet the introduction of chiral surfaces on inorganic nanostructures presents a novel avenue for control. These surfaces, mirroring the chirality of natural enzymes could steer interactions with biological systems and thus, the course of biomedical reactions. Furthermore, they could alter the performance of attached ligands, impacting enzymatic processes. The orientation of these ligands on chiral surfaces could diversify their function, emphasizing the importance of chiral surfaces in imitating enzymatic activity. The focus now lies on enhancing the asymmetric formation of such surfaces during nanostructure synthesis to harness their full potential in catalysis. In addition, Advanced electron microscopy and spectroscopic techniques are anticipated to shed light on the relationship between structure and properties, as well as the underlying catalytic mechanisms, which could spur progress in the research of novel chiral nanomaterials that outperform enzymes in selective catalysis. The design of chiral catalysts with long-term durability also presents a challenge. A comprehensive comprehension of the interplay between electromagnetic fields and the dynamics of charge carrier separation, in conjunction with biocatalytic performance, is essential for the development of high-efficiency chiral nanomaterials for catalysis.

3.2. Biosensing

Optical active nanomaterials have emerged as a cornerstone in the development of advanced sensors, renowned for their exceptional sensitivity, user-friendly operation, minimal toxicity and the capability for both qualitative and quantitative analysis of biomolecules such as proteins and nucleic acids. These chiral inorganic materials have demonstrated their prowess in the detection of an array of biomarkers, encompassing microRNA, DNA, restriction endonucleases, telomerases, adenosine-50-triphosphate and cysteine. The prevalent strategy

in fabricating chiral sensors involves the assembly of nanoparticles into asymmetric chiral structures, which is instrumental in enhancing their sensing capabilities. Moreover, chiral nanosensors have proven to be adept at swiftly and efficiently detecting a variety of metal ions, including zinc, copper, magnesium, lead, mercury and silver. Optical active materials also stand out for their high efficiency and selectivity in the ultrasensitive detection of trace molecules like hydrogen sulfide (H_2S), ROS, mycotoxinsn and so on (Figure 1 Biosensing). These different nanomaterial biosensors have different detection characteristics (Table 2) [16–19]. Chiral biosensors fabricated from these nanomaterials can be categorized into four distinct categories based on their output signals: CD signal biosensors, fluorescent chiral biosensors, colorimetric chiral biosensors and electrochemical chiral biosensors. These categories correspond to alterations in CD signals, fluorescence signals, UV-Vis spectral signals and ratiometric changes, respectively. The choice of sensor is guided by the specific recognition mechanism required for the detection task. In particular, CD signal biosensors have garnered significant interest with chiral assembly being a focal point of research. Sensors prepared via chiral assembly can be broadly divided into two types based on their target's role in the assembly process. The first type involves sensors where the target serves as a link in the chiral assembly or disrupts the chiral linkage, leading to a transformation from an achiral to a chiral assembly or vice versa upon detection of the analyte. The second type features sensors where the target is recognized by a specific recognition unit, such as antibodies or aptamers, which then form a chiral complex enhancing the sensor's response. The CD signals of biomolecules are typically confined to the UV range, whereas those of inorganic nanomaterials can be shifted into the visible or near-infrared spectrum. This shift allows the CD signals from inorganic nanomaterials to avoid interference from biological systems, making them suitable for use as sensing signals within biological environments. Furthermore, the dissymmetric factor (g-factor) values of inorganic nanomaterials can be significantly amplified through mechanisms such as plasmonic coupling, electron hybridization and surface crystal lattice distortion, thereby increasing the detection sensitivity [20,21].

In summary, optical active nanomaterials offer superior sensitivity and specificity compared to other detection methodologies. Their unique geometrical and chiroptical properties are garnering increasing attention for applications in biosensors and diagnostics. However, the complexity of living organisms presents a significant challenge in developing nanoprobes that are accurate, specific and stable enough for use in living systems, particularly for clinical diagnostics. Incorporating protective materials, such as metal-organic frameworks and single-stranded DNA, may offer a viable strategy to address these challenges and enhance the performance and applicability of chiral nanomaterials in biosensing. In addition, grasping the complex interplay between chiral inorganic nanomaterials and biomolecules is critical for developing highly responsive sensors that can detect minute amounts of biological molecules. These innovative sensors, leveraging the properties of optical active nanomaterials could accurately identify diseases in the early, facilitating intervention before conditions worsen.

Table 2. Detection characteristics of biosensors based on chiral nanomathrials.

S No	Biosensors Category	Probes	Detection object	Analytical characteristics	References
1	Small molecules	AuNR@; CMSNPs; Ag@Au core–shell (CS) NPs; MOFs structure (Phe-Cu-PTA); Cys-MoO2/glucose oxidase; D-penicillamine/Cys-CdS QDs	Chiral Cys; Aspergillus ochraceus; Aflatoxin B1; L-Trp; D-Trp; Glucose; L-Pen; D-Pen	high selectivity and high efficiency	[8,9]
2	Metal ion	Au NP heterodimers;D-cysteine capped MoO2 NPs; L-cysteine (Cys) capped MoO2 NPs; CdSe NPLs; Chiral chelating QDs; Chiral carbon dots; Chiral luminescent zinc(1I)-MOF;Tb-MOF	Ag^{+}; Hg^{2+}; Hg^{2+}; Pb^{2+}; Ni^{2+}; Co^{2+}; Sn^{2+}; Fe^{3+}; Fe^{3+};	high sensitivity and high selectivity	[16,17]
3	Macromolecule	Au NPs; Ag@Au CS NP; 3D Au-DNA-hybrid structure	Alpha fetoprotein; 8-hydroxy-20-deoxyguanosine; DNA methyltransferase activity; HER2-positive SK-BR-3 cells; DNA; Small sequences of RNA	mechanism, specificity, and sensitivity of the chiral sensors are determined by specific reactions between biomarkers and linkers (such as aptamer, DNA, and RNA)	[18]

3.3. Nanomedicine

Chiral molecules' selectivity is a key factor in many biological processes, significantly influenced by molecular chirality. Previous research indicates that the *in vivo* behavior of biomolecule-modified chiral nanomaterials is impacted by the chirality of their surface ligands. These ligands' chirality can alter the nanomaterials' biocompatibility and their capacity to modulate cellular signaling pathways (Figure 1 Nanomedicine). These nanomaterials also play a crucial role in immunological responses with left-handed variants showing superior performance as vaccine adjuvants, highlighting the importance of chiral surface interactions in enantioselectivity. Their interaction with CPL introduces dichroic behavior and a g-factor, enabling targeted plasmonic heating for tumor ablation and the generation of ROS for biocatalytic processes. These properties are opening new horizons in gene-editing, stem cell research and therapeutic strategies for diseases like Alzheimer's. Furthermore, chiral ligand-modified nanomaterials exhibit varied toxicities and optical activities, with potential applications in photothermal therapy for cancer treatment and the selective identification and cleavage of double-stranded DNA. Chiral nanoparticles with their potent response to CPL are poised to minimize collateral damage in treatments, leading in a new era of precision medicine [22–24].

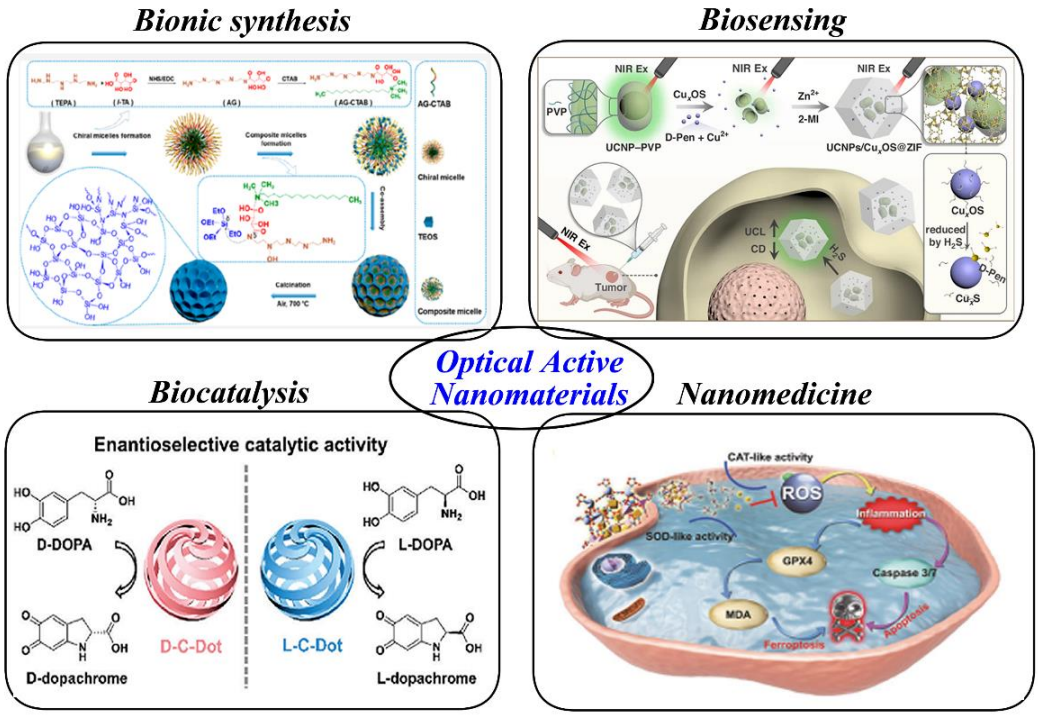

Figure 1. Bionic synthesis: Schematic illustration for the process of creating l-mSiO_2 nanospheres involves the utilization of specially crafted micelles, which possess chiral properties and NH_2-groups, as the foundational components in the organic-inorganic self-assembly technique [10]; **Biocatalysis**: Schematic illustration for the chiral carbon dots exhibit enantioselective catalytic capabilities in the oxidation process of DOPA enantiomers [11]; **Biosening**: Schematic illustration for the working process of biosensing in cells and *in vivo* based on the UCNPs/CuxOS@ZIF nanoprobes [21]; **Nanomedicine**: Schematic illustration for Ptzyme@D-ZIFs alleviate the inflammatory response caused by anabatic conditions by neutralizing reactive oxygen species within cells, thereby reducing cellular harm via pathways involving both apoptosis and ferroptosis [22].

The chirality-dependent physical and chemical attributes of asymmetric inorganic nanomaterials have the potential to influence biological systems at the nanometer scale, including the regulation of specific enzymatic reactions or the initiation of immune responses. Despite their potential, applications at the clinical level have not yet been fully realized due to the current lack of detailed knowledge regarding the interactions between these chiral inorganic surfaces and living organisms. The expansion and refinement of chiral inorganic surface characteristics are vital for enhancing our comprehension of the dynamics at the interface between organic and inorganic substances, which is a critical factor in their practical application in the biomedical field. Chiral gold nanoparticles are capable of altering immune signaling through receptor interactions that vary with the enantiomer, a feature that is closely associated with the nanomaterial's chiral structure. This suggests that an increase in the structural intricacy of these chiral nanomaterials could lead to a greater variety of interactions at the organic-inorganic interface, thereby increasing their potential for use in

biomedical applications, such as cancer immunotherapy, by potentially influencing the dynamics of immune cells and the cycle of cancer immunity.

4. Summary and outlook

Optical active nanomaterials, with their typical biological impacts and versatile characteristics have significantly propelled advancements in fields such as biocatalysis, biosensing and nanomedicine. Despite these advancements, several challenges persist, particularly in the context of their further development and practical application. The synthesis of intrinsically chiral nanomaterials with asymmetric morphology remains challenging, with a current g-factor of 0.4. Enhanced control over nucleation and growth is crucial to significantly increase this value. In addition, optical active nanomaterial biomedical application requires a deeper understanding of their pharmacokinetics, metabolism and distribution in living organisms. Optical active nanomaterials are also being explored as immune system regulators, necessitating a comprehensive study of their interaction with the immune system to improve biocompatibility and reduce cytotoxicity. At the same time, Clinical research is essential to bridge the gap between animal models and human applications, ensuring the safety and efficacy of these materials. Addressing these challenges will pave the way for innovative healthcare solutions, including next-generation drug delivery systems and therapeutic agents.

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Conflicts of interests

The authors declare no competing interests.

Authors’ contribution

M.Z. and S.W. contributed equally to this article. Conceptualization, W.M. and Y.Z.; formal analysis, W.M., H.S., L.Z.; investigation, H.H.; data curation, W.Z.; writing—original draft preparation, M.Z.; writing—review and editing, W.M.; supervision, W.M.; project administration, W.M.; funding acquisition, W.M. All authors have read and agreed to the published version of the manuscript.

References

[1] Zhao L, Chen L, Cheng D, Wu T, Fan Y, *et al.* Potential application prospects of biomolecule-modified two-dimensional chiral nanomaterials in biomedicine. *ACS Biomater. Sci. Eng.* 2024, 10(4):2022–2040.

[2] Ma B, Bianco A. Regulation of biological processes by intrinsically chiral engineered materials. *Nat. Rev. Mater.* 2023, 06(8):403–413.

[3] Cho NH, Guerrero-Martínez A, Ma J, Bals S, Kotov NA, *et al.* Bioinspired chiral inorganic nanomaterials. *Nat. Rev. Bioeng.* 2023, 2(1):88–106.

[4] Yan J, Feng W, Kim J, Lu J, Kumar P, *et al.* Self-assembly of chiral nanoparticles into semiconductor helices with tunable near-infrared optical activity. *Chem. Mater.* 2019, 32(1):476–488.

[5] Pan J, Wang X, Zhang J, Zhang Q, Wang Q, *et al.* Chirally assembled plasmonic metamolecules from intrinsically chiral nanoparticles. *Nano Res.* 2022, 15(10):9447–9453.

[6] Jeong K, Lee D, Tran V, Wang C, Lv J, *et al.* Helical magnetic field-induced real-time plasmonic chirality modulation. *ACS Nano*. 2020, 14(6):7152–7160.

[7] Li Y, Cheng J, Li J, Zhu X, He T, *et al.* Tunable chiroptical properties from the plasmonic band to metal–ligand charge transfer band of cysteine‐capped molybdenum oxide nanoparticles. *Angew. Chem. Int. Ed.* 2018, 130(32):10393–10397.

[8] Yu T, Jing L, Jian Y, Xing KL, Wen LQ. Filled carbon-nanotube heterostructures: from synthesis to application. *Microstructures*. 2023, 3(3):2023019.

[9] Li HX, Wang LT, Yan SM, Chen JL, Zhang MM, *et al.* Fusiform-like metal-organic framework for enantioselective discrimination of tryptophan enantiomers. *Electrochim. Acta.* 2022, 419:140409.

[10] Xu L, Guo M, Hung C, Shi X, Yuan Y, *et al.* Chiral skeletons of mesoporous silica nanospheres to mitigate Alzheimer's β-amyloid aggregation. *J. Am. Chem. Soc*. 2023, 145(14):7810–7819.

[11] Zhang, M, Zhang W, Fan X, Ma Y, Huang H, *et al.* Chiral carbon dots derived from serine with well-defined structure and enantioselective catalytic activity. *Nano Lett*. 2022, 22(17):7203–7211.

[12] Cao H, Yang E, Kim Y, Zhao Y, Ma, W. Biomimetic chiral nanomaterials with selective catalysis activity. *Adv. Sci.* 2024, 11:2306979.

[13] Qiao L, Zhang J, Jiang Y, Ma B, Chen H, *et al.* Near-infrared light-driven asymmetric photolytic reduction of ketone using inorganic-enzyme hybrid biocatalyst. *Int. J. Biol. Macromol*. 2024, 4(264):130612.

[14] Li C, Hang T, Jin Y. Atomically Fe-anchored MOF-on-MOF nanozyme with differential signal amplification for ultrasensitive cathodic electrochemiluminescence immunoassay. *Exploration*. 2023, 3:20220151.

[15] Feng T, Liu J, Zhang X, Fan D, Bai Y. Protein engineering of multi-enzyme virus-like particle nanoreactors for enhanced chiral alcohol synthesis. *Nanoscale Adv*. 2023, 5:6606–6616.

[16] Wang XB, Wang QS, Chen YL, Li JG, Pan RK, *et al.* Metal-to-ligand charge transfer chirality-based sensing of mercury ions. *Photon. Res*. 2021, 9(2):213.

[17] Wang XB, Hao JJ, Cheng JJ, Li JZ, Miao J, *et al.* Chiral CdSe nanoplatelets as an ultrasensitive probe for lead ion sensing. *Nanoscale*. 2019, 11(19):9327.

[18] Funck T, Nicoli F, Kuzyk A, Liedl T. Sensing picomolar concentrations of RNA using switchable plasmonic chirality. *Angew. Chem. Int. Ed*. 2018, 57(41):13495.

[19] Li C, Zhang M, Huang C. A novel approach using copper oxide nanocomposites-based biosensor for lactate detection in athletes. *Alex. Eng. J*. 2024, 10(105):218–229.

[20] Ghorani N, Madani A, Entezar S. Real-time biosensor application of structurally chiral medium for detection and sensing of plasma in human blood. *Phys. Scr*. 2023, 98(5):055518.

[21] Lu Y, Zhao X, Yan D, Mi Y, Sun P, *et al.* Upconversion-based chiral nanoprobe for highly selective dual-mode sensing and bioimaging of hydrogen sulfide in vitro and in vivo. *Light Sci. Appl*. 2024, 8(13):180.

[22] Jiang W, Li Q, Zhang R, Li J, Lin Q, *et al.* Chiral metal-organic frameworks incorporating nanozymes as neuroinflammation inhibitors for managing Parkinson's disease. *Nat. Commun.* 2023, 14(1):8137.

[23] Chen B, Song L, Yuan Y, Liu X, Guo Z, *et al.* Chirality-Dependent Tumor Phototherapy Using Amino Acid-Engineered Chiral Phosphorene. *ACS Appl. Mater. Interfaces*. 2023, 15(1):651–661.

[24] Fang J, Liu D, Xu D, Wu Q, Li H, *et al.* Integrated Au-nanoroded biosensing and regulating platform for photothermal therapy of bradyarrhythmia. *Research.* 2022, 9854342.