Self-assembled organic/metal ion nanohybrids for theranostics

Kai Zhang | Nana Zhao | Fu-Jian Xu

State Key Laboratory of Chemical Resource Engineering, Key Laboratory of Biomedical Materials of Natural Macromolecules (Beijing University of Chemical Technology, Ministry of Education), Beijing Laboratory of Biomedical Materials, Beijing University of Chemical Technology, Beijing, China

Correspondence
Prof. N. N. Zhao, Prof. F. J. Xu, State Key Laboratory of Chemical Resource Engineering, Key Laboratory of Biomedical Materials of Natural Macromolecules (Beijing University of Chemical Technology, Ministry of Education), Beijing Laboratory of Biomedical Materials, Beijing University of Chemical Technology, Beijing 100029, China.
Email: zhaonn@mail.buct.edu.cn; xufj@mail.buct.edu.cn

Funding information
National Key Research and Development Program of China, Grant/Award Number: 2016YFA0201501; National Natural Science Foundation of China, Grant/Award Numbers: 51773013, 51922022, 51733001; Beijing Outstanding Young Scientist Program, Grant/Award Number: BJJWZYJH01201910010024; Fundamental Research Funds for the Central University, Grant/Award Numbers: BHYC1705A, XK1802-2

Abstract
Owing to their remarkable physicochemical and favorable biological properties, self-assembled organic/metal ions nanohybrids show great potential for constructing multifunctional nanoplatfoms of cancer theranostics. By tailoring the structural components of organic blocks and metal ions, various nanoplatfoms with integrated properties can be manufactured. These nanoplatfoms offer different capacities, including high loading effect, facile modification/functionalization, and excellent biocompatibility, which are beneficial for applications in bioimaging and cancer treatments. This review focuses on the design, fabrication, properties of organic/metal ions nanohybrids, and their applications in biosensing, bioimaging, therapy, and bioimaging-guided therapy of cancer. Various research works related to organic/metal ions nanohybrids toward cancer theranostics are highlighted. By presenting and summarizing these research works and discoveries, the species of organic blocks and metal ions are also discussed. The prospects and challenges for future researches in this field are also proposed.

KEYWORDS
biosensing, metal ions, nanohybrids, organic species, theranostics

1 | INTRODUCTION

Cancer, characterized by disordered growth, malignant proliferation, substantial invasion, and spontaneous metastasis, has been regarded as a significant public health problem seriously threatening human health and life.1 Considering the disadvantages of conventional cancer treatment, the emerging “theranostics” combining accurate diagnosis and efficient treatment has displayed significant superiority and a high potential for developing personalized nanomedicine.2

With the continuous and rapid development of nanotechnology, novel and advanced nanoplatfoms for cancer theranostics have received widespread interests.3 Up to now, various theranostic nanoplatfoms have been designed via integrating the high-resolution diagnostic techniques and efficient therapeutic strategies based on the unique physicochemical, biological, optical, magnetic, thermal, and radioactive properties of nanomaterials.4 Particularly, more and more efforts had
been made to develop nanoplatforms with high accuracy, high efficiency, excellent biocompatibility, and minimally invasive tumor diagnosis and therapy is the current hotspot in this research field.

Self-assembled organic/metal ions nanohybrids, constructed by two components of organic building blocks and metal ions, own several unique characteristics, favoring their applications in developing personalized nanomedicine to fight against cancers. Due to the designability and diversity of organic building blocks and metal ions, the intriguing nanohybrids can be fabricated as various functionalized nanosystems. They can be distinguished by morphologies (dot, particle, sheet, shuttle, sphere, etc.), sizes (quantum dots level, nanoscale, macroscale, etc.) and properties (physicochemical, optical, electrical, magnetic, etc.). Different nanoplatforms have been widely used in bio-related applications, including drug delivery, biosensing, bioimaging, and therapy. In particular, self-assembled organic/metal ions nanohybrids with the combination of imaging and therapy can be employed for cancer theranostics. Inorganic metal ions such as Mn$^{2+}$ and Gd$^{3+}$ can introduce the function of magnetic resonance imaging, Fe$^{2+}$ and Cu$^{2+}$ with chemo-dynamic characteristics can induce the generation of high cytotoxic reactive oxide species (ROS), thereby achieving cell apoptosis. The nanohybrids constructed from functional molecule-modified organic blocks can be endowed with new properties, such as photodynamic, fluorescent, photothermal properties, etc. Moreover, the organic components can enhance the biocompatibility and stability of nanohybrids. The further functionalization of nanohybrids also provides in vivo targeting ability and degradability for cancer diagnosis, treatment, and imaging-guided therapy.

To date, a good deal of self-assembled organic/metal ions nanohybrids have been designed through modulating organic components and metal ions coordination. They are widely investigated in drug delivery, biosensing, bioimaging, therapy, and theranostics. To provide a comprehensive outline of recent research progress concerning versatile self-assembled organic/metal ions nanohybrids for cancer theranostics, this review is mainly arranged in the order of design, properties, and several representative works of cancer theranostics (Figure 1). The organic species of nanohybrids are first introduced and classified into two primary types of synthetic organic molecules and biomolecules. Different fabrication strategies of nanohybrids are also presented in this review. Notably, the current research status of multifunctional organic/metal ions nanohybrids, in biosensing for tumor markers and metal ions, imaging for cancer diagnosis and treatments, and imaging-guided cancer therapy, are systematically stated. Finally, the challenges and prospects of self-assembled organic/metal ions nanohybrids are concluded to shed light on their bio-related applications, especially for cancer theranostics.

2 | DESIGN OF SELF-ASSEMBLED ORGANIC/METAL IONS NANOHYBRIDS

In this section, we first present the classification of self-assembled organic/metal ions nanohybrids and the unique properties and significant potential of these nanomaterials in bio-related applications. As an essential part, the general fabrication strategies of various organic/metal ions nanohybrids are also introduced.
TABLE 1 Examples of synthetic organic molecules- and biomolecules-based nanohybrids

| Synthetic organic molecules | Organic ligands          | Metal ions | application | Reference |
|----------------------------|--------------------------|------------|-------------|-----------|
| Imidazole                  | 2-methylimidazole        | Zn(II)     | Gene Therapy | 14        |
| 4,4′,4″-(1H-imidazole-2,4,5-tryl)tripyridine | Ni(II) | Sensor | 22 |
| 2-methylimidazole          | Co(II)                   | Chemotherapy | 23 |
| 3,5-Diphenyl-1,2,4-triazole| Cu(I)                    | CDT        | 24 |
| Porphyrin                  | 5,10,15,20-tetra(p-benzoato)porphyrin | Ti(IV) | PDT | 25 |
|                            | TCPP                     | Zr(IV)     | Fluorescence, PDT | 26 |
|                            | 4-methylphenylporphyrin  | Ti(IV)     | SDT         | 27 |
| Pyridin                    | N-Pyridin-3-yl-2-[4-(pyridin-3-ylcarbamoylmethyl)-phenyl]-acetamide | Cd(II) | Catalysis | 28 |

| Biomolecules | Protein           | Hg(II) | Sensor | 29 |
|--------------|-------------------|--------|--------|----|
| BSA          | Mn(II)            |        | PTT, PAI | 19b|
| peptide      | Mn(II)            |        | PTT    | 30 |
| L-cysteine   | Cu(I)             |        | CDT    | 19a|
| DNA          | G3139             | Fe(II) | Gene Therapy | 31 |
| DNA          | Gd(III)           | Fe(II) | MRI   | 32 |
| DNA          |                  | Gd(III) | MRI   | 33 |
| DNA          |                  | Zn(II) | Gene Therapy | 34 |

2.1 Organic species and properties of organic/metal ions nanohybrids

Since metal ions are positively charged, the organic molecules have been modified by various special functional groups (such as -COOH, -NH₂, -SH, etc.) to provide coordination sites for metal ions in efforts to develop new versatile types of self-assembled organic/metal ions nanohybrids. The species of organic blocks are classified into synthetic organic molecules and biomolecules (Table 1). Synthetic organic molecules exhibit high designability and controllable preparation, with great potentials for fabricating metal ion-coordinated nanohybrids with diverse nanostructures and unique optical, electronic and magnetic properties. Eligible organic ligands usually contain N, O, S, P, etc., which possess a strong electron transfer ability to provide coordination sites to metal ions. Recently, various synthetic organic molecules have been employed to construct organic/metal ions nanohybrids, such as pyridines, porphyrins, imidazoles, phenols, and carboxylic acid-based synthetic organic molecules, which can form stable coordinated connection with metal ions.

Metal–organic frameworks (MOFs) and/or porous coordination polymers (PCPs), as typical organic/metal ions nanohybrids, composed of synthetic organic ligands as struts and coordinated metal ions/ion clusters as joints, have received extensive interests in the past decade, especially in bio-related applications. Due to the diversity and selectivity of organic building blocks and metal ions, MOFs with various features and unique properties can be easily obtained. The wide aperture distribution is ranging from micropores to mesopores or macropores. Highly tunable specific surface areas, as well as the significant rigid/flexible skeletons, make MOFs as ideal candidates for fabricating multifunctional nanoplatforms for cancer theranostics, including biosensing, cargo delivery, bioimaging, and therapy. Diverse functionalized organic molecules have been employed to fabricate new-style MOFs with intrinsic physicochemical properties. For example, porphyrins and porphyrin derivatives that bond with metal ions to form MOFs have been used as photodynamic agents for cancer therapy. Imidazolate modified-organic molecules and Zn²⁺ ions were used to construct zeolitic imidazolate MOFs (ZIF-8), which could respond to the acidic tumor microenvironment (TME) and be degraded for efficient drug release. Meanwhile, in coordination with functional inorganic metal ions, MOFs can be endowed with novel properties, such as Mn²⁺ for MRI, and Fe²⁺ for chemo-photodynamic therapy (CDT) of cancer.

Biomolecules usually endow organic/metal ions nanohybrids with intrinsic biocompatibility and excellent stability, especially in a biological system. In particular, owing to their abundant constitutional units, such as four types of deoxyribonucleotides for DNA, four types of ribonucleotides for RNA, more than 20 types of amino acids for protein, the self-assembled organic/metal ions nanohybrids exhibit...
high versatilities. Proteins as a class of critical functional biomolecules participate in various life activities, including enzymatic reactions, electron transfer, and metal transport via the capacity of coordinated metal ions or metal complexes in the biological system. Various protein-based organic/metal ions nanohybrids regarded as artificial metalloproteins have been developed by metal coordination in protein scaffolds, favoring the design of new-style nanoplatforms for bio-related applications. Several tumor-targeted protein-based nanohybrids as contrast agents for cancer diagnosis have been developed via the immobilized metal ions with imaging functions to specific proteins. The proteins with the interior spaces such as ferritin or hemoglobin also can be employed as templates to accumulate iron ions to form nanohybrids, which can prevent the oxidation of free ferric ions.

DNA, an exquisite design of natural biomolecule with superior properties including nanometric dimension, relatively high physicochemical stability and great mechanical rigidity of non-single strand, acts as one of the most promising candidates for self-assembly nanomaterials. A single DNA strand enables assembly of defined double, triple, quadruple strands, or branched structures via specific noncovalent hydrogen-bonding (termed as “Watson–Crick” base-pairing principle). As a result, programmable self-assembled nanoscale networks can be achieved. When the hydrogen-bonding “Watson–Crick” base pairs are replaced by metal ions and/or metal complexes interactions immobilized inside DNA double helix, the “metal–base pair” is formed. Up to now, various monovalent and multivalent metal ions, such as Ag+, Mn2+, Hg2+, Zn2+, Gd3+, etc., have been employed to bridge the skeletons of DNA double helix to fabricate metal ions/DNA nanohybrids. These nanohybrids exhibit high rigidity/flexibility, good biocompatibility, strong stability, and efficient tumor-targeting capacity, providing excellent potential for the design of novel systems of cancer theranostics.

2.2 Preparation methods of organic/metal ions nanohybrids

With the development of advanced synthetic strategies, abundant organic/metal ions nanohybrids with diverse morphologies and controllable particle diameters have been successfully fabricated to meet the increasing demand in bio-related applications. In this section, we will briefly introduce the fabrication strategies of organic/metal ions nanohybrids.

Till now, various efficient methods for preparing self-assembled organic/metal ions nanohybrids have been developed. Generally, room-temperature nanoscale precipitation, solvothermal method, microwave-assisted method, and continuous flow synthesis are explored (Table 2). Room-temperature nanoscale precipitation is employed to synthesize amorphous organic/metal Ions nanohybrids by using the insolubility of nanoparticles and the solubility of precursors. This method was utilized to prepare flavonoid-metal ion complexes constructed by metal ions and flavonoid with pharmacological properties and therapeutic activities, such as quercetin/Fe(II). Solvothermal synthesis is regarded as the straightforward and typical approach for self-assembled organic/metal ions nanohybrids with lattice structure by using a solution of metal ions and ligand treated with high temperature and high pressure, resulting in easily controlled particle nucleation, crystal, and growth. However, this synthetic method has several inevitable disadvantages, such as a large amount of organic solvents, prolonged reaction time, and harsh reaction conditions.

Burgeoning nanotechnology and instruments promote the development of emerging fabrication strategies for organic/metal ions nanohybrids, including microwave-assisted methods, and continuous flow synthesis. These strategies avoid the disadvantages of hydro/solvothermal synthesis and obtain organic/metal ions nanohybrids with the required size and structures in short reaction times or mild reaction conditions (Table 2). Some examples of synthetic nanohybrids from different synthesis methods are reported in Table 3. For biomolecule-based nanohybrids, the preparation procedures are usually performed in a unique reaction buffer to maintain their physiological structure and biological activities. For example, protein–metal ion nanohybrids can be formed in an alkaline reaction solution, in which the metal ions can be covalently bound to the amino acid residues on the surface of protein molecules. To prepare DNA-based nanohybrids, the metal ions can insert into DNA double helix through the substitution of canonical “Watson–Crick” base pairing by a coordinative metal–base pairing in the phosphate buffer or Tris-HCl buffer. Meanwhile, due to the different affinity between various metal ions and the four types of bases, such as Hg2+ and Ag+ to T–T and C–C, Zn2+/Co2+/Ni2+ to G at high pH, versatile DNA/metal ion nanohybrids have been developed in bio-related applications.
**TABLE 3** Examples of organic/metal ions nanohybrids from different synthesis methods

| Method                                | Organic ligands                                    | Metal ions | Application      | Reference |
|---------------------------------------|----------------------------------------------------|------------|-----------------|-----------|
| Room-temperature nanoscale precipitation | c,c,t-(diamminedichloro-disuccinato)Pt(IV)          | Tb(III)    | Drug Delivery   | 41        |
|                                       | 2-methylimidazole                                   | Zn(II)     |                 | 42        |
|                                       | thiazolidine 2, 4-dicarboxlic acid                   | Cu(II)     | Sensor          | 43        |
| Solvothermal                          | Fe-TCPP                                            | Zr         | PTI, PDT       | 44        |
|                                       | TCPP                                               | Cu(II)     | PDT             | 45        |
|                                       | H2DBP                                              | Hf(IV)     | PDT             | 46        |
|                                       | TCPP-Pd                                            | Co(II)     | PDT             | 47        |
| Microwave-assisted methods            | 1,3,5-benzenetricarboxylic acid                     | Tb(III)    | Sensor          | 48        |
|                                       | cyanopyridine                                      | Cu(III)    | Photocatalysis  | 49        |
|                                       | 4,4′-biphenyldicarboxylic acid                     | Zr(IV)     | Catalysis       | 50        |
|                                       | H3(BTB)                                            | Zn(II)     | Catalysis       | 51        |
| Continuous flow synthesis             | BSA                                                | Zn(II)     | Chemotherapy    | 52        |
|                                       | 1,4 benzenedicarboxylic acid                       | Zr(IV)     |                 | 53        |
|                                       | H3BTC                                              | Cu(II)     |                 | 54        |
|                                       | H3BTC                                              | Zn(II)     |                 | 54        |

3 | SELF-ASSEMBLED ORGANIC/METAL IONS NANOHYBRIDS FOR THERANOSTICS

3.1 | Organic–metal ions nanohybrids for biosensing

Sensitive detection of the types of physiological species and dynamic monitoring of their concentration changes in vitro or in vivo will contribute to diagnosing diseases and revealing the underlying pathological mechanisms. Therefore, designing multifarious biosensors with the capacity of sensing biomarkers is significant for developing biomedicines and treatment strategies of diseases. Due to the high loading capacity, facile functionalization, excellent biocompatibility, and stability of self-assembled organic metal ions nanohybrids, these nanohybrid-based biosensors exhibit superiorities of high sensitivity, good selectivity, and low limit of detection (LOD). In this section, we principally introduce the applications of biosensors based on organic/metal ions nanohybrids to detect different biological species, including biomacromolecules (DNA, RNA, antigen, etc.), small molecules (glucose, \( \text{H}_2\text{O}_2 \), \( \text{H}_2\text{S} \), etc.), and metal ions. The abnormal expressions of these molecules are related to various diseases. Therefore, a great deal of organic/metal ions nanohybrid-based biosensors have been fabricated for the detection of nucleic acids and proteins. Recently, DNA strands can be incorporated on the surface of MOF through electrostatic interactions, p–p stacking or chemical bonding to construct MOF-based nanoprobes for the detection of DNA, RNA, and proteins. For example, Li et al. designed three types of DNA hairpin strands-modified UiO-66 MOF fluorescent nanohybrids for multiple DNA detection in a homogeneous solution. When the targets were recognized by DNA hairpin probes, significantly enhanced fluorescence signals could be obtained due to the high loading capacity of UiO-66 MOF. The DNA-responsive MOF nanohybrids exhibited a sensitive detection of targets with a low LOD of 20 fM and specific discrimination of single-base mismatch (Figure 2A,B).

Catalytic DNA molecules (termed as DNAzyme) are regarded as a class of DNA/metal ions complexes, which can promote DNA or RNA cleavage at a signal ribonucleotide base when specific metal ions recognize and insert into the double-stranded DNA sequences. As an emerging enzyme-free detection strategy, metal ion-specific DNAzyme exhibits high potentials to fabricate multitudinous biosensors for biomolecules detection owing to its designability, versatility, and high catalytic efficiency. MicroRNAs (miRNAs), a class of endogenous small molecule RNAs, are related to various biological processes and the occurrence of major diseases, especially human cancer, which can be regarded as potential...
diagnostic and prognostic biomarkers. Due to the good affinity of DNA double helix to metal ions and the porosity of DNA hydrogels, Zhang and co-workers incorporated DNA-capped Au nanoparticles and their complementary fluorescent DNA sequences into a hydrogel network to achieve the high loading effect of hairpin-locked DNAzyme strands and active metal ions. This nanoprobe was explicitly responsive to intracellular multiplex miRNAs through strand-displacement reaction and metal ions-assisted DNAzymes dual signal amplification, assessing the abundance of multiplex cancer-related miRNAs in different cells (Figure 2C–F). Moreover, hemin-bridged MOF interface, through double amplification procedures of G-quadruplex payload and DNAzyme catalysis nanoprobe, was designed for ultrasensitive lasting chemiluminescence miRNA imaging with a LOD of 1 fM.
Interestingly, UiO-66 MOF can efficiently identify phosphorylation sites, favoring the enrichment of phosphorylated peptides. Yan and co-workers utilized UiO-66 as highly efficient affinity probes to a fabricate rapid and straightforward fluorescence-based biosensor for protein kinase activity analysis. Under the optical experiment, the increased fluorescence intensity was directly proportional to the protein kinase A activity with a low detection limit of 0.00005 μL. This sensing platform was employed for protein kinase activity detection in drug-stimulated MCF-7 cell lysates, demonstrating its potential and universal applicability in kinase-related research. Meanwhile, DNAzyme motor was also applied for amplified detection of proteins. Zhang et al. reported a self-powered and target-triggered Mg2+-dependent DNAzyme motor that could autonomously walk along hundreds of substrate strands decorated Au nanoparticles. This assay could be employed to detect streptavidin and thrombin.

### 3.1.2 | Small molecules detection

Glucose is an important energy molecule, which plays a critical role in cellular metabolism, and is regarded as a biomarker for disease diagnosis. Xiao et al. proposed iridium metal ions complex doped polystyrene electrophilic optical fibrous membrane and further functionalized the nanohybrids with glucose oxidases (GOD/EOF), to fabricate a quick and highly sensitive optical biosensor. In the presence of glucose, its yellow luminescence (562 nm) was significantly enhanced, even at a shallow glucose concentration. The sensing platform exhibited a wide concentration ranging from 3.0 × 10^{-10} M to 1.3 × 10^{-10} M and a low detection limit of 1.0 × 10^{-10} M, superior to that of other reported glucose biosensors. Moreover, Zhou’s group synthesized 2D Co-TCPP(Fe) nanohybrids with peroxidase activity, which could catalyze hydrogen peroxide (H2O2) decomposition to generate hydroxyl radical (•OH) and further oxidized luminol and produce a strong chemiluminescence signal. Therefore, by loading luminol and glucose oxidase (GOD), a simple chemiluminescence-functionalized sensor Co-TCPP(Fe)@luminol@GOD was obtained for rapid glucose detection. Under optimized conditions, this Co-TCPP(Fe)@luminol@GOD sensor exhibited good performance with a good LOD of 10.667 μg/L in a wide range of 32–5500 μg/L (Figure 3A, B). Moreover, this sensing platform could be employed to screen glucose in various human urine samples from hospitals.

H2O2, as a main member of ROS and a byproduct of oxidase enzymes-assisted catalytic reaction, plays a vital role in various biological activities. The abnormal concentration level of H2O2 can induce many diseases. Yang and co-workers designed ZIF-8 framework-reduced and graphene oxide-supported bimetallic AuPt nanoparticles (AuPt/ZIF-8-rGO) as a novel peroxidase mimic for H2O2 detection. The nanoparticle showed an enhanced peroxidase-like catalytic capacity for electrochemical H2O2 detection in a wide concentration range of 100 Nm to 18 mM and a very low detection limit of 19 nM. Biocompatible adenosine triphosphate (ATP) as the ubiquitous energy conversion molecules in organisms has multiple functional groups, exhibiting an outstanding ability to coordinate with many metal ions. Qiu et al. synthesized novel cerium coordination polymer nanohybrids ATP-Ce-Tris by using ATP molecules as the biocompatible ligands to Ce3+ ions. The ATP-Ce-Tris nanohybrids could be employed as artificial peroxidase for the selective and sensitive detection of H2O2 with a detection limit down to 0.6 nM, depending on the oxidation of the fluorescent ATP-Ce(III)-Tris to non-fluorescent ATP-Ce(IV)-Tris by H2O2. Moreover, this sensing platform was extended to the detection of glucose in combination with the specific catalytic effect of glucose oxidase for the oxidation of glucose and the formation of H2O2 (Figure 3C–E).

Monitoring and quantifying the concentration levels of various gases is significant in the disease diagnosis and clinical medicine. For example, H2S is an important class of biomolecules in living organisms. Jose’s group developed 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) vesicles embedded with Cu2+ ions complex receptor (1.Cu) for H2S detection. The H2S sensing platform was established through a metal indicator displacement process, and Eosin-Y was employed as an indicator. The naked eye confirmed the high selectivity by distinguishing reactive sulfur species, reactive nitrogen species, biological phosphates, and other anions. The high sensitivity with a lower detection limit of 4.06 μM was also achieved from systematic fluorescent titration. The application of this vesicular receptor for real sample analysis was also confirmed by fluorescence living cell imaging.

### 3.1.3 | Metal ions detection

Metal ions, as essential elements in the human body, play vital roles in maintaining cellular activities and human health. An excess of metal ions can harm body health, especially heavy metal ions that can quickly accumulate in the human body and induce functional impairment of organs. Therefore, it is of great importance to sensitively and specifically detect metal ions. Considering that some MOFs can generate strong luminescent signals with visible emission colors, lanthanide-based MOFs can be developed as promising chemical sensors for metal ions or organic small molecules. Zhang and co-workers successfully assembled a new luminescent terbium-based MOF [Tb3(L)2(HCOO)(H2O)5]⋅DMF·4H2O (Tb-MOF) composed of Tb3+ ions and pyridyl-tetracarboxylate. The Tb-MOF exhibited highly selective and sensitive sensing of Cu2+ ions, and its luminescence was nearly entirely quenched in
DMF solution and biological system. Furthermore, some researchers utilized specific base-pairs to capture metal ions and fabricate sensors to detect metal ions, such as T–T for Hg$^{2+}$ forming as T-Hg(II)-T, C–C for Ag$^{+}$ forming as C-Ag(I)-C, and Pb$^{2+}$-stabilized G-quadruplex (Figure 4A).70 Chen et al. prepared a biosensor composed of a 2D MOF and T-rich single-stranded P-DNA probe for the succession sensing of Hg$^{2+}$ and I$^{-}$, yielding detection limits of 3.2 for Hg$^{2+}$ and 3.3 nM for I$^{-}$, respectively (Figure 4B).71

Moreover, genetically encoded fluorescent proteins have been widely used for metal ions detection.72 Tang et al. described a strategy utilizing the combination of infrared fluorescent protein (IFP) and its chromophore as an infrared fluorescence probe for detecting Hg$^{2+}$.29 Hg$^{2+}$ possessed specifically binding affinity to a cysteine residue (C24) of IFP, and inhibited the conjugation of IFP chromophore biliverdin (BV) to C24, resulting in “turning off” the infrared emission of IFP. This assay showed high selectivity toward Hg$^{2+}$ among other metal ions over a broad pH range and in vitro detection limit of ∼50 nM. Additionally, the IFP/BV sensor could serve as a tool to detect Hg$^{2+}$ in living organisms or tissues.

### 3.2 | Organic–metal ions nanohybrids for imaging diagnosis

Bioimaging provides a visual device for the real-time and dynamic tracking of lesions, benefiting accurate diagnosis of...
earlier diseases. Various imaging modalities, such as fluorescence imaging (FLI), photoacoustic imaging (PAI), magnetic resonance imaging (MRI), and positron emission tomography (PET) imaging, have been proposed for bioimaging. Imaging contrast agents with excellent properties and good biocompatibility are necessary to generate signals at the targeted tissues or enhance the signal contrast between tumors and surrounding tissues. Due to their diverse compositions, tunable structures, and facile functionalization, organic–metal ions nanohybrids have been widely employed in bioimaging. In this section, we highlight some organic–metal ion nanohybrids based platforms as imaging contrast agents or contrast agent carriers applied in bioimaging.

### 3.2.1 Fluorescence imaging

The superiorities and characteristics (such as high sensitivity, high stability, and low toxicity) promote FLI to be one of the most critical technologies in optical biological imaging. Due to the unique photochemical properties, especially optical property, porphyrins and porphyrin derivatives have been widely used to construct various optical devices. Karam et al. reported zirconium-based nanohybrids (MOF-525) encapsulated carboxyphenyl porphyrin (TCPP-H2) with high light stability. After receiving continuous irradiation, the fluorescence intensity of MOF-525 showed an insignificant change (2%), whereas the fluorescence intensity of free porphyrin samples decreased to 16%. The porphyrin molecules encapsulated by MOF could significantly enhance its light stability. However, traditional porphyrin molecules were excited by light with short wavelengths, which limits their applications in bioimaging of deep tissue. To address the issue, Yang et al. developed a nanoplatform by covering ultra-small titanium dioxide nanoparticles on a heterodimer consisting of up-conversion nanoparticles (UCNPs) and porphyrin-based nanohybrids (PCN-224). This nanoplatform could be used for tumor imaging due to the presence of porphyrin MOF and the light conversion effect of UCNPs.

### 3.2.2 Photoacoustic imaging

PAI is regarded as one of the fastest growing non-invasive and non-ionizing hybrid imaging technologies, showing better imaging depth, higher spatial resolution, and higher contrast compared with optical imaging. The porosity and tunable structures of MOF-based nanohybrids impart them with excellent internal and external loading capacities, inducing the effective delivery of photoacoustic conversion reagents with MOF. Chen et al. utilized the remarkable encapsulation ability of traditional MIL-100 MOF nanohybrids to load curcumin efficiently. Then, polydopamine-modified hyaluronic acid (HA-PDA) was coated to the surface of MOF to improve the dispersibility and stability of the curcumin-loaded MOF, conferring tumor-targeting capability to the nanosystem. The multifunctional nanoplatform showed two-stage enhanced photothermal conversion capabilities, endowing its strong photoacoustic conversion effectiveness. Recently, Chen and co-workers developed an activated intelligent imaging platform based on nanozyme-mediated 2,2′-azidobis(3-ethylbenzothiazolin-6-sulfonic acid) supported ABTS®@MIL-100/poly(vinylpyrrolidone) nanoreactors (AMP NRs) for PAI. The AMP NRs could be
activated specifically by the TME through a nano-enzyme-based “two-step rocket launch-like” process to turn on their photoacoustic signals. These remarkable properties of AMP NRs suggested their potential applications for the development of intelligent, accurate, and non-invasive bioimaging diagnosis and real-time monitoring of treatment processes (Figure 5A,B).

3.2.3 Magnetic resonance imaging

MRI is a non-radiative imaging technique that uses the signals generated by the resonance of atomic nuclei in a magnetic field to reconstruct the image, showing the advantages of better spatial resolution, higher soft-tissue contrast, and infinite penetration depth. Paramagnetic metal ions (such as Gd (III), Mn(II)) are commonly used as contrast agents to improve image contrast and imaging quality. Since these ions possess specific biological toxicity, efficient encapsulation, and delivery of these ions is the actually hot issue of current research. Given the modular nature of MOF, its composition and structure can be easily adjusted by the rational selection of metal ions and organic linkers to obtain MR-enhanced MOF with high biocompatibility and low toxicity. Lin et al. reported the synthesis of Mn-MOFs, which were coated with a thin silica gel shell and further functionalized with acyclic arginine-glycine-aspartate (RGD) peptides and fluorophores to accomplish tumor-specific enhanced MRI.80

Natural biomolecule-based organic/metal ions nanohybrids demonstrate high potential for new insights into the development of MR contrast agents, which show high biocompatibility and good tumor targeting in vivo. Lee and co-workers reported DNA-Mn nanohybrids using DNA polymerization. Under the phi 29 DNA polymerase-assisted rolling circle amplification, single-stranded DNA copies were obtained, and large pyrophosphate anions were generated,
driving self-assembly of DNA-metal ions nanohybrids via “two-metal-ion” mechanism. In particular, DNA-Mn nanohybrids were synthesized, showing significant potential and desirable properties for cell tracking and MRI. Additionally, Tan et al. designed a novel MRI contrast agent by using a cyclic peptide CC9 with a sequence of Cys(disulfide bridge)-Ser-Thr-Asn-Pro-Lys-Val-Leu-Cys(disulfide bridge), which could target cell membrane of mesenchymal stem cells (MSCs) coupled with Gd-DOTA to fabricate Gd-DOTA-CC9 nanohybrids.\(^{78}\) Then Gd-DOTA-CC9 nanohybrids labeled human MSCs (hMSCs) were obtained through electroporation, which could induce cell-assembly of Gd-DOTA-CC9 hybrids in the cytoplasm, significantly promoting cell-labeling efficacy and intracellular retention time. The GdDOTA-CC9 labeled hMSCs could be observed with dark contrast in vivo MRI after intracranial transplantation, which persisted over 12 days (Figure 5C).

3.2.4 | Positron emission tomography

PET is currently the only new imaging technology that can show the metabolism of biomolecules, receptors, and neural mediators in vivo. Compared with other imaging technologies, PET has excellent detection sensitivity, deeper signal penetration, and good quantification capabilities.\(^{79}\) Hong et al. proposed intrinsic radioactive UiO-66 MOF nanohybrids fabricated by positron emission isotope zirconium 89 (\(^{89}\)Zr-UiO-66).\(^{79,80}\) \(^{89}\)Zr-UiO-66 was further functionalized with Pyr-derived polyethylene glycol (Py-PGA-PEG) and coupled with peptide ligand (F3), which could recognize nucleolin for targeting triple negative breast tumors. The functionalized \(^{89}\)Zr-UiO-66 nanohybrids showed strong radiochemistry and stability in different biological media to achieve cell targeting and in vivo PET imaging (Figure 5D). In addition to \(^{89}\)Zr, \(^{65}\)Cu can also be used for non-invasive PET imaging. Zheng et al. reported a high-yield (>95\%) procedure for PET imaging of \(^{64}\)Cu metal ions incorporated into porphyrin bilayer liposome nanovesicles.\(^{82}\) The flexible and powerful radiochemistry provided a range of promising clinical applications for \(^{64}\)Cu-porphyrins nanohybrids, especially in PET imaging probes and radiation therapy.

3.2.5 | Multimodal imaging

Compared with the monomodal bioimaging method, multimodal imaging provides higher accuracy, a more comprehensive evaluation basis, and broader applications for disease diagnosis. The self-assembly integrated organic molecules and metal ions with different functions into one nanohybrid play significant roles in bioimaging with multimodal imaging capacities. Feng et al. proposed a series of photomodal materials, based on the fabrication of metal ions and tannic acid (MITA).\(^{83}\) \(^{53}\)Fe, \(^{53}\)V, and \(^{51}\)Ru based MITA showed excellent photothermal conversion efficiency (\(\eta \approx 40\%\)). Due to the adhesive nature of MITAs, various MITA-based nanoplatforms were readily available. This work validated the efficacy of nanovesicle for multimodal imaging depending on tumor-specific photoactivation, including photothermal imaging, PAI, and \(T_1\)-weighted MRI (Figure 6).

Interestingly, the high loading capacity of organic-metal ions nanohybrids endows them to efficiently deliver functional molecules, which enriches the role of imaging functions. Xie et al. successfully integrated a photosensitive tetrametric chlorin ligand into the Hf-UiO-66 nanohybrids (TCPC-UiO).\(^{84}\) The high photothermal conversion efficiency of Hf element in TCPC-UiO, excellent light stability and biocompatibility, together with strong X-ray attenuation ability provided great potential for multimodal bioimaging containing computed tomography (CT) imaging, photothermal imaging, and PAI, which could enhance the accuracy of disease diagnosis. Additionally, MOFs-based nanohybrids can also be used as a modified part to improve the functional diversity and biocompatibility of nanoplatforms. Tian et al. developed small-sized core-shell Au@MIL-88 (Fe) nanoplatforms modified with poly (ethylene glycol)-carboxylic acid (PEG-COOH) to prevent coagulation during in vivo experiments.\(^{85}\) This core-shell nanocomposite exhibited CT enhancement and PA properties from Au nanorod cores and \(T_2\)-weighted MRI properties from MIL-88 (Fe) nanohybrid shells. This nanocomposite could be applied for highly enhanced CT imaging, MRI, and PAI in glioma in vivo.

3.3 | Organic–metal ion nanohybrids for cancer therapy

Since healing is considered as the ultimate goal, novel nanomedicines for high-efficiency disease treatment are necessary and significant. Currently, a variety of therapy modalities, such as photodynamic therapy (PDT), photothermal therapy (PTT), chemotherapy, radiotherapy, gas therapy, and gene therapy, have been widely studied for disease therapy.\(^{86}\) Meanwhile, to enhance therapeutic efficacy, multimodal therapy strategies have been proposed.\(^{87}\) The emerging organic–metal ion nanohybrids were explored as various therapeutic nanoplatforms with high biocompatibility and versatility. In this section, the biological application of organic–metal ion nanohybrids in disease therapy will be highlighted by some typical research works, including monotherapy such as PDT, PTT, chemotherapy, radiotherapy, and gene therapy, and multimodal therapeutic protocols.
3.3.1 Photodynamic therapy

PDT, as a class of noninvasive phototherapy, has gradually developed as an alternative to chemotherapy, radiotherapy, and surgery. The mechanism of PDT is based on photosensitizers activated by light to induce the generation of highly cytotoxic ROS (including singlet oxygen ($^1O_2$), superoxide anion radical (O$_2$$^{-}$•), and $^{•}$OH), which triggers cell apoptosis and necrosis to eliminate tumors. Compared with other traditional treatments such as chemotherapy and radiotherapy, PDT has minimally invasive characteristic and spatiotemporally controlled ability. However, owing to the hydrophobicity, poor optical stability, and too-low tumor tissue selectivity, the traditional organic small-molecular photosensitizers tend to aggregate, leading to ineffective tumor location enrichment to seriously hinder the efficacy of PDT. The development of nanotechnology provides a great promising way to overcome these restrictions and improve the efficiency of PDT by delivering photosensitizer molecules precisely to the tumor location. Organic–metal ion nanohybrids can passively accumulate in the desired site of actions through enhanced permeability and retention effect, and also can actively target the ideal position by functionalization with target molecules.

In 2014, Lin et al. reported the pioneered work of an Hf ion-based porphyrin-MOF nanohybrid as a highly efficient nano-photosensitizer to fight against head and neck cancer. The novel Hf ion-based porphyrin-MOF (DBP-UiO) was constructed by Hf$^{4+}$ and 5,15-di(p-benzoate)porphyrin (H$_2$DBP), as the first time to realize the delivery of PDT agents using porphyrin-based MOF. Interestingly, the DBP-UiO plate of 10 nm in thickness was ideally suitable for transporting $^1O_2$ from the MOF interior to the cell cytoplasm to exert cytotoxic effects. In this work, an unprecedentedly high porphyrin-based device could be achieved for highly effective PDT of difficult-to-treat cancers. However, the therapeutic efficacy of PDT via Type II mechanism depending on the concentration of O$_2$ is diminished in hypoxic microenvironments of solid tumors. It is crucial to develop PDT protocols via O$_2$-independent Type I mechanism, which generates cytotoxic radicals via electron transfer (ET) from excited photosensitizers to O$_2$ and organic molecules. Recently, Lin’s group synthesized new MOF nanohybrids (Ti-TBP) composed of Ti-oxo chain secondary building units (SBUs) and photosensitizer 5,10,15,20-tetra(p-benzoate)porphyrin (TBP) ligands for hypoxia-tolerant type I PDT (Figure 7A). Upon light irradiation, Ti-TBP not only sensitized $^1O_2$ but also transferred electrons from excited TBP$^*$ species to Ti$^{4+}$-based SBUs to afford TBP$^{•+}$ ligands and Ti$^{3+}$ centers, thus propagating the generation of superoxide and $^{•}$OH. Ti-TBP-mediated PDT elicited a superb anticancer efficacy with >98% tumor regression and a 60% cure rate.

The size of nanoparticles is an essential factor in improving the PDT efficiency. However, the relatively large sizes of current MOF-based nanohybrids usually lead to inefficient...
body clearance and undesirable PDT effect. To overcome these issues, Ren et al. obtained ultrasmall Zr ions-based porphyrinic MOF QDs with high resistance against complicated physiological conditions via a liquid-phase exfoliation route.\cite{89} These MOF QDs held an average hydrodynamic diameter of 4.5 nm, which was below the renal filtration threshold of 5.5 nm. More importantly, due to the ultra-small size of MOF QDs, $^{1}{\text{O}_2}$ generated from the interior of MOFs could totally diffuse out of the frameworks effectively to process the anticancer function. In vivo results indicated that MOF QDs were mainly excreted from mice through kidneys after intravenous administration with low side effects (Figure 7B).

### 3.3.2 Photothermal therapy

PTT, a thermal therapeutic protocol induced by converting near-infrared light energy to high temperature, has been extensively explored as a promising alternative approach for disease treatment. As a critical factor of PTT, photothermal agents could absorb photon energy and dissipate through nonradioactive decay such as heating. A sufficient rise in temperature at the tumor site leads to irreversible necrosis and apoptosis of cancer cells. In principle, PTT is a cancer treatment that targets the location of the tumor, but meanwhile, it causes relatively compromised damage to surrounding healthy tissue.\cite{91} Although pure organic or inorganic metal photothermal agents have good photothermal conversion efficiency, the single functionality of organic molecules and the potential for long-term toxicity of noble metals limit their applications. Alternatively, assembled nanoparticles of organic molecules and metal ions provide advantages such as low toxicity and functional controllability.\cite{92}

Yan’s group developed biomolecule-based nanohybrids as a stable photothermal nano-agent self-assembled by containing BV, metal-binding short peptides and Mn$^{2+}$ ions.\cite{30} Such BV-based nanohybrids could selectively accumulate in tumor location to induce locally tumor temperature increase under mild NIR irradiation, achieving effective photothermal tumor ablation with good biocompatibility. Recently, dynamic protein-metal ions supermolecular nanohybrids can be used as a template to construct protein-based nanohybrids with a high photothermal effect. Liu and co-workers proposed a unique approach based on dynamic protein-metal ion nanohybrids to fabricate adaptable protein-based hydrogel networks.\cite{18b} Through the introduction of Bi$^{3+}$/bovine serum albumin (BSA) supramolecular nanohybrids, Bi$_2$S$_3$-BSA nanoplatform hydrogels had been successfully synthesized and exhibited an excellent photothermal effect. The temperature of Bi$_2$S$_3$-BSA nanoplatform could increase to 75°C under an 808 nm laser irradiation within 10 min in vivo, making it a potential candidate for PTT-based platform against tumors.

Additionally, Zhang’s group developed a living and biohybrid photothermal therapeutic platform of PTB (photothermal bacterium)@ZIF-90/MB,\cite{90} which presented preferential tumor-targeted capacity and enhanced photothermal tumor...
ablation ability. Bacterium *Shewanella oneidensis* MR-1 (*S. oneidensis* MR-1) was employed to introduce sodium tetra-chloropalladate (Na2PdCl4) into palladium nanoparticles (Pd NPs) on the bacterial cell surface to obtain the photothermal effect. Simultaneously, photosensitizer methylene blue loaded ZIF-90 (ZIF-90/MB) was further synthesized and conjugated on the surface of photothermal bacterium (PTB) to obtain PTB@ZIF-90/MB, which could enhance the PTT efficacy of PTB (Figure 7C–E). The aforementioned studies were focused on designing novel nanomaterials for PTT under the irradiation of the first NIR (NIR-I) window light (650–950 nm). Recently, the second NIR (NIR-II) window laser (1000–1700 nm)-induced PTT based on photothermal agents are received wide concerns by researchers, due to their deeper tissue penetration and higher maximum permissible exposure as a respective result of reduced tissue scattering and lower energy of photons at longer wavelengths. Therefore, it is a great challenge and prospect for developing organic–metal ion nanohybrids-based NIR-II photothermal agents for deeper deep-tissue PTT with high photothermal conversion effect.

### 3.3.3 Gene therapy

Gene therapy refers to the introduction of normal foreign genes into target cells to correct or compensate for diseases caused by defects and abnormal genes, achieving disease treatment. Arpita Poddar et al. encapsulated the green fluorescent protein plasmid into the ZIF-8 MOF, which could maintain the functional activity of genes. The gene-loaded nanohybrids enabled them to remain in the cell for 4 days. The expression of functional activity, intracellular transfer, and entrapment genes occurred in a relatively long time without any obvious cytotoxicity. This nanoplatform could maintain the functional activity of DNA plasmid and produce specificity and persistence at the level of in vivo treatments.

Due to the unique metal ion-dependent and sequence-specific cleavage features, DNAzymes not only have been widely used as a useful signal amplified strategy for biosensing, but also considered as a promising therapeutic agent for gene therapy of cancers. Wang et al. fabricated a versatile Zn2+ ions-specific DNZzyme loaded ZIF-8 MOF nanoplatforms for self-sufficient gene therapy. This nanosystem exhibited efficient intracellular delivery and pH-responsive release of DNAzyme molecules, which led to the DNAzyme-mediated inhibition of EGR-1 and resulted in the mRNA cleavage induced gene therapy (Figure 8A). Self-assembly of divalent metal ions (such as Zn2+, Ca2+, and Mg2+) and DNA or siRNA for nanohybrids depend on the interaction between these metal ions with the phosphate backbone of DNA or siRNA. Owing to the diversity and designability of the DNA or siRNA sequence, DNA (siRNA)-based nanohybrids show high potential for gene therapy. Bull and co-workers designed Zn ions/DNA nanohybrids with efficient and homogeneous delivery of a large copy number of nucleic acids into cells. These nanohybrids were capable of facilitating DNA expression or siRNA uptake in various cell types. The Zn/DNA nanohybrids had an excellent capacity to regulate gene expression in living cells and could be used as a gene therapeutic agent for cancer therapy.

### 3.3.4 Other therapies

Radiotherapy is one of traditional cancer therapies, utilizing the interaction between ionizing radiation and tumor tissue to induce cancer cell apoptosis. As a generally recognized mechanism, radiotherapy can cause irreparable damage to tumor cells by breaking the DNA double-strand. Radioactive metal or heavy metal usually exhibits the ability of cancer radiotherapy, such as Au-base materials, Hf metal ions, Cu metal, etc. Liu and co-workers reported Hf-MOF nanohybrids self-assembled by the coordination of Hf4+ metal ions and tetraakis(4-carboxyphenyl)porphyrin (TCPP). In these nanohybrids, Hf4+ metal ions served as a radiosensitizer to enhance radiotherapy effect owing to its strong X-ray attenuation ability, showing a remarkable antitumor effect in vitro and in vivo. Recently, a lot of evidence indicate that hypoxic TME significantly weakens the therapeutic effect of radiotherapy. It is of great significance to improve tumor oxygen partial pressure and enhance radiotherapy. Chen et al. designed a porphyrin-based MOF combined with Au nanoparticles to form MOF-Au nanocomposite and achieve oxygen enhanced radiotherapy. This nanoplatform could enhance the response of hypoxic cancer cells to X-ray and endow MOF with relative stability to prevent premature degradation in the delivery process. The nanoplatform could alleviate the lack of oxygen in tumors, significantly inhibit tumor growth, and reduce systemic toxicity (Figure 8B).

Chemodynamic therapy, utilizing transition-metal-based nanomaterials to catalyze H2O2 to generate high cytotoxic •OH, such as Fe-containing or Cu-composing nanoplatforms, has been developed as an efficient strategy for cancer therapy. Recently, Li et al. constructed self-assembled Cu-amino acid mercaptide nanohybrids (Cy-Cys) through the coordination of Cu2+ ions and sulfhydryl-group-containing L-cysteine, which could accomplish in situ GSH-activated and H2O2-reinforced chemodynamic therapy of drug resistant breast cancer. Cu-Cys nanohybrids could first react with local GSH in cells, induce GSH depletion, and reduce Cu2+ to Cu+. Subsequently, the generated Cu+ reacted with local H2O2 to produce high cytotoxic •OH via a Fenton-like reaction and induce tumor cell apoptosis. Due to the high GSH and H2O2 concentration in tumor cells, Cu-Cys nanohybrids exhibited high cytotoxicity to cancer cells with an
observably efficient tumor inhibition rate of \(\sim 72.3\%\). Meanwhile, various \(\text{Cu}^{2+}\) ions-based MOF nanohybrids responsive to TME have been developed for cancer chemodynamic therapy.98

pH-responsive nanocarriers for a pH-sensitive drug delivery have been widely employed in cancer therapy, owing to the acid TME compared with neutral normal tissues. Tsung et al. designed pH-responsive ZIF-8 MOF nanohybrids for controllable chemotherapy of cancer.95 Negatively charged fluorescein camptothecin (CPT) was encapsulated into the ZIF-8 nanohybrids by simple electrostatic adsorption. The performance of pH-responsive release was driven by the acidic designated target. The cells treated with CPT-ZIF-8 showed stronger cytotoxicity than those without CPT treatment (Figure 8C).

3.4 | Organic–metal ions nanohybrids for theranostics

The rapid development of bioimaging based on functionalized nanomaterials provides an ideal visualization platform for real-time monitoring of the therapeutic processes and dynamic tracking of tumor lesions. Imaging-guided therapy nanoplatforms integrated by bioimaging capacities and therapeutic properties have received intense attention as a promising strategy to maximize the therapeutic effect. With the exploration of the organic–metal ions nanohybrids in bio-related applications, various nanohybrids have been employed as imaging-guided therapy nanoplatforms due to their multi-functionalized structures and composites with excellent imaging properties and therapeutic
In this section, we highlight some organic-metal ion nanohybrid-based nanoplatforms in monomodal and multimodal imaging-guided therapy.

### 3.4.1 Monomodal bioimaging-guided therapy

#### FLI-guided therapy

Liu and co-workers reported multifunctional hybrid nanospheres integrated by Fe$^{3+}$ ions, aggregation-induced emission (AIE) photosensitizer (TPEDCC), and B-cell lymphoma 2 (Bcl-2) inhibitor of sabutoclax by a simple self-assembly way in aqueous media. Fe$^{3+}$ ions were utilized to overcome the tumor hypoxia by inducing ROS and O$_2$ generation via a Fenton-like reaction, whereas the intracellular PDT resistance of the AIE photosensitizer was mitigated by sabutoclax, resulting in enhanced PDT. The multifunctional organic/Fe$^{3+}$ nanohybrids platform had great potentials for image-guided enhanced PDT under the hypoxia TME (Figure 9A). Porphyrin-based MOF nanohybrids have been easily fabricated for FLI-guided therapy due to the combined properties of fluorescence and photosensitizer from porphyrin molecules. recently, Yang et al. constructed a multifunctional nanocomposite composed of ultra-small titanium dioxide nanoparticles, upconversion nanoparticles, and porphyrin-based MOF nanohybrids (UMOF-TiO$_2$), which realized multimodal enhanced PDT by the combination of Type I and Type II mechanisms. The UMOF-TiO$_2$ nanocomposites exhibited the capacity of FLI in vivo and could be employed for FLI-guided effective multimode PDT with deep penetration and good biocompatibility.

#### MRI-guided therapy

Feng and co-workers reported theranostic “nanogenes” by organically integrating Gd(III) as MR contrast agents, double-
stranded DNA as genetic therapeutics, and cracked cancer cell membrane (CCCM) as targeting molecules. The surface enveloped by cancer cell membrane fragments enabled host-specific targeting of the nanogene to the source of cancer cells and homologous tumors while effectively inhibiting recognition by macrophages. The Gd(III)-involved nanogenes generated a much higher $T_1$ relaxation rate than the clinically used Gd-based MRI agents. The Gd/DNA@CCCM nanogene showed great potentials in the host-specific MRI-guided gene therapy.

Encouraged by the development of natural biomineralization, Li’s group reported a biomimetic nanoplatforms for systemic codelivery using one-pot supramolecular self-assembly of a DNA therapeutic (G3139), chemotherapeutic drug DOX, and Fe$^{2+}$ ions (DOX/Fe-G) via multiple coordination interactions. The DOX/Fe-G was further mineralized with a thin shell of ZIF-8 MOF to obtain the final core-shell structured nanoplatform, named as DOX/Fe-G@Z. Due to the combined effect of gene therapy and chemotherapy, the tumor growth was suppressed entirely by DOX/Fe-G@Z, suggesting that the nanoplatform enabled MRI-guided combined treatment of gene therapy and chemotherapy.

**PAI-guided therapy**

Yang et al. synthesized versatile MOF nanohybrids comprising bacteriochlorin ligand as an organic building block and Hf$_6$($\mu_3$-O)$_4$($\mu_3$-OH)$_4$ clusters as metal joint (DBBC-Uio) for efficient PDT under hypoxic TME. The resultant DBBC-Uio nanohybrids could generate abundant superoxide anion radical ($O_2^{•−}$) via Type I mechanism, part of which transformed to high toxic $•OH$ and $O_2$ through superoxide dismutase (SOD)-mediated catalytic reactions under severe hypoxic microenvironment (2% $O_2$) for achieving the $O_2$ recycle. Owing to the synergistic effect of $O_2^{•−}$ and $•OH$ radicals, advanced antitumor performance with highly efficient hypoxic solid tumor ablation in vivo were realized. Furthermore, tumor-specific PAI was also verified for accurate cancer diagnosis with deep tissue penetration and high spatial resolution. This DBBC-Uio was utilized as a specific $O_2^{•−}$-independent PDT therapeutic agent under the hypoxic TME and a PAI agent for bioimaging (Figure 9B).

**3.4.2 Multimodal imaging-guided therapy**

Due to the inherent disadvantages of monomodal imaging-guided therapy, such as limited sensitivity, low tissue penetration or insufficient resolution, multimodal imaging has been proposed to address these issues, which enables more comprehensive information for accurate diagnosis and efficient treatment. Yang and co-workers designed multifunctional zirconium-ferriporphyrin MOF (Zr-FeP MOF) nanoshuttles containing Zr$_6$ cluster as the metal joint and H$_4$TBP-Fe as organic building blocks via a facile one-pot hydrothermal method (Figure 9C). The Zr-FeP MOF nanohybrids could generate abundant $•OH$ by Fenton reaction and $^{1}O_2$ with a NIR laser irradiation. The photothermal conversion efficiency was calculated to be 33.7%. PA signals was observed in the tumor station after injection of Zr-FeP MOF into tumor-bearing mice. Furthermore, the nanoshuttles exhibited good CT capability owing to the high-Zr component for CT imaging. By loading siRNA, an inhibitor of heat shock protein 70 (Hsp70), the siRNA/Zr-FeP nanoplatform was employed for combined treatment of PDT and low-temperature PTT under a single NIR laser irradiation. Such fascinating “all-in-one” nanoagents with tri-modal imaging and combined PDT/PTT would be a powerful tool for precise tumor diagnosis and imaging-guided therapy. Additionally, Yan and co-workers constructed a supramolecular nanoplatform (FMCNP$\alpha$s) containing amphiphilic amino acid (9-fluorenylmethyloxycarbonyl-L-leucine, Fmoc-L-L), MRI contrast agent ($Mn^{2+}$), and photosensitive drug (Ce6) via a simple self-assembly way (Figure 9D). The cooperative biometal-organic nanohybrids enabled enhanced PDT to damage tumor cells and tissue by efficiently delivering Ce6 and improving the reductive TME via the competitive coordinative of GSH with $Mn^{2+}$. The amino acid or peptide-tuned multicomponent synergetic self-assembled nanohybrids could be regarded as a promising approach to develop “all-in-one” nanomedicines with improved diagnostic precision and therapeutic efficacy.

**4 CONCLUSIONS AND PERSPECTIVES**

So far, diverse and multifunctional self-assembled organic/metal ions nanohybrids have explored as nanoplatforms for disease theranostics. The fabrication strategies of these nanohybrids rely on the coordination between the functional groups in organic molecules and the passive charges of multivalent metal ions in different reaction conditions. Due to the designability of organic molecules and numerous choices of metal ions, versatile organic/metal ions nanohybrids have been continuously developed to meet increasing demands. Furthermore, by regulating reaction conditions, optimal nanohybrids with appropriate sizes, morphologies, physicochemical properties, and functional capacities are employed in bio-related applications, including biosensing, bioimaging, disease treatment, and imaging-guided therapy.

In addition to the adjustable structures and physicochemical properties, organic–metal ions nanohybrids exhibit good biocompatibility ensued by selecting alternative components and raw materials with hypotonicity or nontoxicity. Further functionalization of the components renders nanohybrids biodegradability and excludability, which can enhance their
biological performances. The facile surface modification of organic–metal ions nanohybrids by using biomolecules such as proteins or targeting molecules ensures their good biosecurity and actively accumulation in the target location, achieving enhanced performances in bio-related applications. The high loading capacity of nanohybrids enables them to deliver various functional molecules, including detection probes, imaging agents, and therapeutic drugs. To sum up, self-assembled organic/metal ions nanohybrids exhibit significant superiorities in biological applications of biosensing, imaging for diagnosis and various therapies.

Although numerous advances on organic/metal ions nanohybrids had been achieved, some critical challenges still remain in bio-related applications. For example, the raw materials for constructing nanohybrids should be simple, cheap, stable, repeatable, and controllable. When the nanohybrids are injected into living organisms, the appropriate circulation time, active/passive accumulation effect, and tumor-specific internalization are of great importance, which will directly affect the efficiency of imaging and therapy. Additionally, the interactions between nanohybrids and tumor tissues, as well as the cellular uptake efficiency, are also essential issues, especially for the internal tissues of solid tumors. In a word, although organic/metal ions nanohybrids are promising candidates for biomedical applications, their structures and properties should be optimized to meet the requirements of clinical disease theranostics.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENT
This work was supported by the National Key Research and Development Program of China (grant no. 2016YFA0201501), National Natural Science Foundation of China (grant nos. 51773013, 51922022, and 51733001), Beijing Outstanding Young Scientist Program (project no. BJJWZYJH01201910010024), and the Fundamental Research Funds for the Central University (project nos. BHYC1705A and XK1802-2).

ORCID
Fu-Jian Xu https://orcid.org/0000-0002-1838-8811

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AUTHOR BIOGRAPHIES

Kai Zhang earned his Ph.D. degree in materials science and engineering from University of Science and Technology Beijing, China in 2020 under the supervision of Prof. Zhou Yang and Prof. Haifeng Dong. Then he became a postdoctoral researcher and joined Prof. Fu-Jian Xu’s group at Beijing University of Chemical Technology. His current research focuses on design, synthesis, and biological application of nanoscale metal–organic frameworks.

Nana Zhao is currently a professor at Beijing University of Chemical Technology. She obtained her Ph.D. degree in physical chemistry from Peking University, China in 2008 under the supervision of Prof. Limin Qi, and was a postdoctoral scholar with Prof. Eugenia Kumacheva at the University of Toronto, Canada and Prof. Lutgard De Jonghe at Lawrence Berkeley National Laboratory. She was a recipient of National Science Foundation for Outstanding Youth Science Foundation (NSFC, 2019). Her current research focuses on design, synthesis, and application of versatile organic–inorganic nanohybrids.

Fu-Jian Xu is currently a professor at Beijing University of Chemical Technology. He received his Ph.D. degree in biomolecular engineering from National University of Singapore in 2006. He was a recipient of National Science Foundation for Distinguished Young Scholars (NSFC, 2013) and Cheung Kong Distinguished Professor (Ministry of Education of China, 2014). His current research focuses on the design, construction, and application of functional biomacromolecules.