Materdicine: Interdiscipline of materials and medicine

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Abstract
The clinical medicine and biomaterials are two fields that are conducive to achieving the goal of precise medicine on diagnostics and therapeutics of various diseases. The interdiscipline of materials and medicine, termed/abbreviated as “materdicine,” seeks to address the dominant medical shortcomings and challenges faced by conventional medicine, including inferior bioavailability, systemic toxicity, poor targeting specificity, and unsatisfied diagnostic/therapeutic efficacy. In this review, we present the perspective and discussion on the use of diverse biomaterials for disease diagnosis and treatment from a broad perspective, especially on nanoscale biomaterials. We initially highlight the recent advances on the engineering of abundant contrast agents for diagnostic bioimaging, such as optical fluorescence imaging, magnetic resonance imaging, and photoacoustic imaging. In addition, discussions on the diagnostic biosensing for point-of-care diagnosis, such as fluorescent and plasmonic sensors, are supplemented. Furthermore, we outline several materdicine-enabled therapeutic modalities for disease treatments, including the following exemplified scaffold biomaterials for regenerative medicine. Especially, rational modulation of toxicity issues of micro-/nanoscale biomaterials is also accounted for addressing the possible concerns of biocompatibility and biosafety on further clinical translation of materdicine. Finally, we summarize facing challenges and outlook future developments relating to the clinical translation of these distinctive biomaterials in materdicine.

KEYWORDS
bioimaging, biosensing, materdicine, regenerative medicine, therapy, toxic effects

1 INTRODUCTION

Numerous medical problems are still unresolved at current stage, as validated by a large amount of people who are still suffering from various chronic or acute diseases.1 Despite tremendous worldwide endeavors have been devoted to conquering these medical issues, chronic diseases such as diabetes,2 obesity,3 vascular diseases,4 and cancer5 are still prevalent around the world, severely endangering the health of human beings without obvious indications of controllable signs. Moreover, some infectious diseases, such as human immunodeficiency virus (HIV), malaria,
and tuberculosis, remain major global health concerns, primarily impacting millions of people from underprivileged sections in modern societies and underdeveloped countries. Generally, the solutions to these major global public health issues require the integrative efforts of multiple advanced technologies.

Micro- and nanotechnologies are rapidly evolving and provide new possibilities to address prevention, diagnosis, and treatment of various diseases. In particular, a variety of micro-/nanoscale biomaterials, including polymeric nanoparticles, carbon nanotubes, metallic nanoparticles, quantum dots, liposomes, hydrogels, and inorganic nanoparticles, have been extensively explored in the past decades. The physicochemical properties (sizes, shapes, surface chemistry, and chemical composition) of these biomaterials have been engineered in the microscale and nanoscale range to enable distinctive features, leading to tunable optical, magnetic, electronic, and acoustic properties and biological effects. Their intrinsic features facilitate the rapid development of contrast agents (CAs), delivery vehicles, therapeutic agents, diagnosis devices, and medical devices for precision medicine. In addition to the micro-/nanoscale biomaterials, a large number of three-dimensional (3D) bulk biomaterials have been developed and fabricated for extensive biomedical applications at preclinical or clinical stages, such as the scaffolds or implants for localized tissue treatment or tissue regeneration. Therefore, the interdisciplinary integration between materials science and medicine, termed as “materdine” (abbreviated and combined term of materials and medicine), offers new opportunities to jointly deal with complicated issues in the field of medicine by the progress of material science. Materdine refers to the design and fabrication of biomaterials/medmaterials with the direct application purpose/requirement originating from the clinical problems and challenges, which will be further directly used in solving the facing critical issues of clinical medicine. Therefore, the interdisciplinary materdine dominantly focuses on the clinical medicine requirement, and quickly satisfies the specific medical requirement by employing the corresponding biomaterial-based platforms and technologies.

Despite micro-/nanoscale biomaterials hold profound promise in clinical medicine, their clinical translation has been relatively slow, as compared to abundant bulk biomaterials in materdine that have been extensively used in clinic such as tissue regeneration biomaterials. For instance, there are only about 200 products based on micro-/nanotechnologies that have been approved by Food and Drug Administration (FDA) or under clinical trials. Several reasons are considered to account for this slowness, covering the challenges in fabricating high-yield micro-/nanomaterials with high repeatability, insufficient comprehension of the relationship between the intrinsic physicochemical features of these materials and their in vivo behaviors/effects, and the paucity of approaches on screening biomaterials that predict their behaviors in vivo. Especially, successful translation use in clinical medicine is a challenging process, requiring substantial preclinical investigations, well-chosen clinical indexes, rational design, and completion of clinical trials.

Materdine is the design and direct application of biomaterials in medicine, striving to address diverse medical challenges and weaknesses faced by traditional medicine, which cover inferior bioavailability, systemic toxicity, poor target specificity, and unsatisfied therapeutic efficacy. Especially encouraged by the discovery from various “natural” nanoparticles in the body, including nanosized lipids, proteins, vehicles, and key biomacromolecules, which can act as delivery vehicles and/or regulate the natural functions in the body, a wide range of nanoscale materials have been rationally tailored for medical use very recently. In the earlier examples of materdine, polymer- and lipid-based delivery carriers with encapsulated drug molecules have been elaborately engineered for targeted and sustained drug release. Meanwhile, an increasing concern regarding medical uses of inorganic, organic, and organic/inorganic hybrid nanoparticles, possessing unique features at the micro/nano scale, has resulted in a burst of research interests in developing multifunctional probes for contrast-enhanced bioimaging and disease diagnosis. Moreover, materdine-mediated diagnostic and therapeutic medicines were considered as the complementary technologies that resulted in unprecedented advances in theranostic medicine. Additionally, other medical techniques that crucially depend on the advances of materdine have been extensively explored accompanying with a large number of biomaterial categories, including biosensing, tissue engineering, and so forth.

The rapid development of interdisciplinary collaborations between materials science and medical researchers is crucial to the success in dealing with complex problems in the diagnosis and treatment of diseases. On this ground, this review proposes and highlights the perspective of materdine, providing a deep discussion on the rational design, construction, and application of versatile biomaterials/medmaterials with unique physiochemical property and specific biological effects for disease diagnosis and treatment from a broad perspective (Figure 1). Based on the thousands of available progresses and publications of the materdine applications in disease theranostics, this review only selectively discusses some representative paradigms and examples to reveal and clarify the approaches and strategies on the biomedical applications of versatile biomaterials in materdine. Of course many important progresses are not involved in this
review, because there are also many excellent and important reviews available for summarizing and discussing some specific aspects of biomaterials in biomedicine. It is herein aimed to exemplify representative and extensively explored biomaterial systems/platforms in materdicine and clarify the underlying perspective of materdicine. For instance, we present a summary and discussion on the engineering of various diagnostic imaging agents/probes for optical fluorescence imaging, magnetic resonance imaging (MRI), and photoacoustic (PA) imaging. In addition, we discuss the recent advances in diagnostic biosensing in materdicine, such as fluorescent and plasmonic sensors, for point-of-care (POC) diagnosis of various diseases. Moreover, clarification on several therapeutic strategies, such as photodynamic therapy (PDT), photothermal therapy (PTT), sonodynamic therapy (SDT), and magnetic hyperthermia therapy (MHT), for disease therapy is also accounted. Especially, we outline the recent progresses on the construction of scaffold biomaterials, such as hydrogels, 3D printing scaffolds, and biomimetic scaffolds, for regenerative medicine. The chemical control of toxicity of micro-/nano-sized biomaterials (size, morphology, surface chemistry, and chemical composition) is also exemplified to show how to address the concerns of the biocompatibility and biosafety of versatile biomaterials in materdicine. We also summarize the very recent advances/progresses in the field of materdicine, and outlook some of the translational challenges and critical issues related to the clinical use of materdicine in disease treatments.

2 | MATERDICINE IN BIOIMAGING

Early detection and efficient treatment of diseases are of crucial significance for raising the survival rates of patients with serious illness. In vivo bioimaging techniques, which facilitate the doctors to observe deeply within living organisms, are providing enormous opportunities for clinical diagnosis. As a powerful research tool to realize early diagnosis of various diseases, the fundamental goal of noninvasive bioimaging is to detect and localize specific molecular targets, physiology, and pathways under the circumstance of a disease state. Diseases are generally recognized by the accumulation of CAs and simultaneous signal output at the disease regions in CA-enhanced bioimaging, attributing to the fundamental biology difference between diseased tissues and normal tissues. The conventional CAs, such as radioisotopes or organic dyes conjugated with peptides, proteins, antibodies, or aptamers, are currently utilized in clinical applications. Nanomaterials in materdicine, as molecular probes and CAs, are receiving considerable interests in the applications of molecular imaging, biosensing, and medical diagnostics due to their peculiar features, including magnetic, optical, and electronic properties as well as high chemical/thermal stability. Furthermore, nanomaterials can be easily and precisely engineered to implement multiplex functions via delivering payloads, such as integration with therapeutic agents. To compete efficiently against small-molecule CAs, nanomaterials must cause negligible biosafety risk after in vivo administration, while furnishing at least one substantial superiority, such as improved resolution, augmented imaging sensitivity, or multiplexing capability. Currently, the representative nanomaterial-based imaging modalities in clinical settings or preclinical research include MRI, positron emission tomography (PET), single-photon emission computed tomography, computed tomography (CT), optical fluorescence imaging, PA imaging, and ultrasound (US) imaging.

2.1 | Magnetic resonance imaging

MRI is one of the commonly used imaging modalities in clinical diagnosis due to its high temporal and spatial resolution, tunable soft-tissue contrast, and lack of ionizing radiation. MRI relies on the monitoring of nuclear magnetic resonance signals, which are generally produced by the relaxation of the protons in various physiological environments in the presence of a magnetic field. The variations in relaxation times, either longitudinal (T1) or transverse (T2), are highly determined by the protons located in tissues. However, owing to the low sensitivity of MRI
technique, a high local concentration of CAs is required to achieve enhanced MRI signals. Paramagnetic metal ions (e.g., Gd$^{3+}$ and Mn$^{2+}$) can be employed to markedly strengthen the performance and detection capability of MRI through affecting the MRI signals of neighboring tissues.\textsuperscript{23b,39} Therefore, to improve the detection resolution and sensitivity of MRI, a dizzying array of diverse nanomaterials have been engineered by incorporating the classic CAs into nanomaterials to guarantee that large amounts of paramagnetic metal ions can be effectively delivered to the desired sites.\textsuperscript{39c,40}

Ultrasmall iron oxide nanoclusters (USIONCs) (<4 nm) have been received substantial attentions owing to their prominent capability in T1 MRI contrast enhancement.\textsuperscript{41} Comparatively, the aggregation of iron oxide nanoparticles can alter relaxation times of protons, leading to a dramatic T2 MRI contrast enhancement. Therefore, T2/T1 switching was achieved by modulating the aggregation states of USIONCs.\textsuperscript{42} For instance, a pH-responsive iron oxide nanocluster assembly (RIA) was elaborately designed by modifying i-motif DNA-originated pH-responsive linkers on the surface of USIONCs (Figure 2A).\textsuperscript{43} The hydrodynamic diameter of RIA was reduced from 120 to 20 nm with the pH changing from 7.4 to 5.5 (Figures 2B and 2C). Meanwhile, an increased brightness in the MRI phantom images and a drastic decline in the $r_2$ relaxivity were observed with the decrease of pH value. In vivo T1 MRI was performed on a hepatocellular carcinomas (HCC) model. The brightening of HCC and the simultaneous darkening of normal liver facilitated highly sensitive diagnosis of HCC.
Optical fluorescence imaging

Fluorescence imaging technique has been extensively explored in bioimaging, which provides highly selective, real-time, and direct signals of biospecimens. However, conventional fluorescence imaging in vivo confronts with limited penetration depth and low spatial resolution, attributing to the large light absorption and photon scattering in biological tissues in the visible and first near-infrared (NIR-I) regions. Fluorescence imaging in the second NIR (NIR-II, 1000-1700 nm) biowindow has been developed as an alternative strategy for in vivo imaging with ever-escalating research interests. Benefited from the diminished background autofluorescence and minimized photon scattering in the NIR-II biowindow, NIR-II fluorescence imaging in vivo provides unique superiorities, such as deeper tissue penetration depth, improved imaging fidelity, and enhanced spatial resolution, in contrast to that of conventional fluorescence imaging. In the past decades, tremendous efforts have been devoted to exploiting NIR-II-emitting fluorophores for in vivo imaging of deep-seated diseases, including small-molecule organic fluorophores, single-walled carbon nanotubes, quantum dots, and rare-earth-doped nanocrystals.

In comparison with the available NIR-II fluorophores, rare-earth-doped nanocrystals with more prominent photostability and higher biosecurity are competent to generate intense NIR-II emission. To achieve improved NIR-II fluorescence imaging performance under an excitation of a NIR-II laser, Tm$^{3+}$-sensitized NaYF$_4$:Tm$^{3+}$/Er$^{3+}@$NaYF$_4$ nanocrystals with the excitation and emission wavelengths at 1208 and 1525 nm, respectively, were fabricated for multiplexed encoding and decoding (Figure 3A-C). On account of the significant cross-relaction effect of neighboring Tm$^{3+}$-Tm$^{3+}$ and Tm$^{3+}$-activators, fluorescence lifetimes of the activators (Er$^{3+}$, Ho$^{3+}$, and Yb$^{3+}$) could be precisely modulated by regulating the content of Tm$^{3+}$ (Figure 3D). For instance, with the increasing doping content of Tm$^{3+}$, the fluorescence lifetimes of these fluorophores at 980, 1180, and 1525 nm could be effectively reduced to 0.24, 0.78, and 0.36 ms, respectively (Figures 3E and 3F). Furthermore, colloidal NaErF$_4@$NaYF$_4$: x%Tm$^{3+}@$NaYF$_4$ nanocrystals were adopted as a luminescent ink to fabricate and implant two-dimensional QR codes for in vivo encoding and decoding. By comparing with steady-state fluorescence imaging system, high-resolution images with high signal-to-noise ratio were obtained using this time-gated fluorescence system (Figure 3G-J). This work not only pioneers a new avenue to the exploitation of luminescent materials with both excitation and emission in the NIR-II region, but also provides a novel multiplexed encoding strategy for information storage and decoding in vivo.

PA imaging

PA imaging, as an emerging hybrid imaging modality, harvests the superiorities of optical and US imaging through direction of laser pulses into a sample and reception of acoustic waves to create PA images. The laser in/acoustic-signal out paradigm facilitates the detection depth up to 5 cm at a higher spatial resolution compared to conventional optical fluorescence imaging in biological tissues. Because PA imaging capability is highly dependent on thermoelastic expansion, the photothermal conversion performance of a PA agent is crucial to its output PA signal. Exogenous PA agents with absorption in the NIR region can be used to strengthen the PA signal, due to a low scattering coefficient and a relatively low absorption coefficient within NIR region, thus furnishing a relatively clear window for PA imaging. In the past decades, various intelligent activatable nanomaterials have been developed as PA probes that are off until they are activated by biomolecular targets in living animals for in vivo PA imaging of diseases.

Matrix metalloproteinase (MMP)-2 is a crucial biomarker that overexpresses in numerous solid tumors in various cancers, such as bladder, breast, colon, stomach, and prostate cancers. Therefore, the evaluation of MMP-2 activity in vivo is crucial to early diagnosis and efficient treatment of cancers in clinic. To address this crucial issue, a NIR fluorophore(Cy5.5) and a quencher(QSY21) were covalently conjugated with a MMP-2-cleavable peptide sequence to establish an activatable PA probe (denoted as QC) for quantitative analysis of the MMP-2 activity in breast cancers (Figure 4A). The self-assembled QC nanoparticles displayed negligible fluorescence but were promptly activated by MMP-2 to emit intense fluorescence. Importantly, the intensity of PA signal at 680 nm decreased in a MMP-2 concentration-dependent manner (Figure 4B). However, the intensity of PA signal at 730 nm was independent of MMP-2 concentration. The ratiometric PA signals ($\Delta$PAS$_{680}/\Delta$PAS$_{730}$) at the tumor site reached the equilibrium at 1.5 h postinjection after the sustained increase at the initial stage (Figure 4C-E). Furthermore, the expression level of MMP-2 declined against the tumor size (Figures 4F and 4G). Consequently, this unique performance allowed quantitative detection of the expression level of MMP-2 in vivo.
The past decades have witnessed tremendous strides in the field of diagnostic imaging in vivo. Biomaterials exhibit considerable superiorities relative to small-molecule bioimaging probes and fill the gap between small-molecule and large-sized imaging probes. Nevertheless, sustained endeavors are urgently required to uncover the underlying imaging mechanisms and provide guidance to design the next-generation nanomaterial-based probes for ultrasensitive imaging. For in vivo applications, concerns regarding long-term biosafety, simplified synthetic approaches, and scale-up strategies should be addressed before entering the clinical trial stage.

3 MATERDICINE IN BIOSENSING

Plenty of pathological processes in various organs and tissue are accompanied by a series of variations in biological indexes, such as pH, ions concentration, temperature, and redox states. Hence, the development of biosensors for signal capturing is conducive to the comprehension of intricate biological processes and realization of precision diagnosis. Biosensors are mainly composed of a bioreceptor that discerns analytes and produces signals, a transducer that translates the signals into measurable electronic pulses, and a reader that presents the signals in a displayable style. Among diverse categories of biosensors, nanomaterial-based counterparts have revealed their tremendous potential to satisfy the requirements of clinical diagnosis, attributing to their fascinating features of high sensitivity and selectivity, reproducibility, simplicity of operation, and low cost of analysis. Especially, a nanoplatform with a high surface area can facilitate surface binding of various recognition moieties to efficiently capture analytes, thus achieving efficient and sensitive detection. Currently, a wide range of spectroscopic
techniques, such as fluorescence, Raman, absorption, and plasmonics, have been employed to quantify molecular information for in vitro diagnosis. Among these, fluorescent and plasmonic biosensors have been extensively utilized, which are exemplified and discussed in this section to clarify the materdicine application in biosensing.

3.1 Fluorescent biosensors

Fluorescent biosensors employ diverse fluorescence parameters, including variations in fluorescence intensity, shifts in fluorescence emission peak, ratiometric changes of the fluorescence intensities at two different emission peaks, or changes in fluorescence lifetime, to identify and detect analytes. Biorecognition moieties of fluorescent biosensors play crucial roles to translate the information of analytes into distinguishable variations of different fluorescence parameters. Fluorescence-based biosensing has been extensively applied to monitor the biological activities in living cells for disease profiling at cellular level. The fluorescence biosensors on the strength of quantum dots and upconversion nanoparticles are purposely selected and briefly discussed in this section to show the materdicine use in fluorescent biosensors.

Nanobeacons (NBs), as intriguing biosensor to detect nucleic acids in living cells, are anticipated to improve the specificity and sensitivity of molecular biosensing.
However, the valencies of most QD-based NBs cannot be easily controlled, thus diminishing their specificity and sensitivity for single RNA detection and imaging. To address this issue, a distinctive type of QD-based NB with controllable valencies has been established by precise conjugation of a black hole quencher (BHQ1) and a phosphorothioate co-modified DNA molecule onto the surface of QDs via a one-pot hydrothermal approach (Figure 5A).\(^7\) This QD-based NB was validated to be effective in labeling and detecting low-abundance nucleic acids in living cells (Figure 5B). In addition, single HIV-1 RNA could also be efficiently detected in live HIV-1-integrated cells (Figure 5C). Furthermore, QD-based NB was utilized to label HIV-1 genomic RNAs, which was then encapsulated in progeny viral particles for tracing the dynamic uncoating process of a single virus (Figure 5D-F). The developed QD-based NB with controllable valencies furnishes a versatile nanoplatform for intracellular nucleic acid labeling and sensing with high sensitivity, particularly for tracing individual RNAs.

Upconversion nanoparticles can be excited by NIR laser and emit visible luminescence for visualization, manifesting enormous potential in biosensing. The feasibility to fabricate small-sized multicolor upconversion nanoparticles facilitates them to be used as available biosensors for multiplexed biosensing.\(^7\) Especially, upconversion nanoparticle-based biosensors are highly effective in detecting biochemical substances as well as in accurately monitoring fundamental biological processes with high selectivity and sensitivity.\(^7\)

Benefiting from the favorable features of upconversion nanoparticles in biosensing, a sensitive biosensing platform, abbreviated as LUCID (luminescence compact in vitro diagnostics), was constructed for point-of-care (POC) molecular and cellular biosensing (Figure 6A-E).\(^7\) The luminescence lifetime of upconversion nanoparticles was prolonged by regulating their structures and compositions (Figure 6A). A compact, filterless imaging device using optimized upconversion nanoparticles as luminescent reporters was built on a smartphone (Figure 6C-E). Highly sensitive detection of a wide range of biological targets was demonstrated. For instance, LUCID achieved effective detection with high sensitivity (0.5 and 0.1 pM for protein and nucleic acids, respectively), differentiation of bacterial species, and screening of cancer cells (Figure 6F). In proof-of-concept clinical application, cervical brushing specimens were subjected to LUCID for cancer-cell screening (Figure 6G). Patients
can be differentiated into three categories, including “high risk,” “low risk,” and “benign” (Figure 6H). The development in upconversion nanoparticle-based biosensing propels LUCID as a versatile diagnostic tool to meliorate healthcare delivery in resource-limited surroundings.

### 3.2 Plasmonic biosensing

A localized surface plasmon resonance (LSPR) sensor, as a sensitive technique, can be utilized for biosensing by recording the shifts in LSPR peaks. The oscillation of surface plasmon is highly sensitive to the adjacent dielectric circumstances. Surface plasmon resonance (SPR) sensors, as one type of commercially available plasmonic biosensors, use the delocalization of SPR at the interface of a thin metallic film.

Plasmonic biosensing techniques utilize metal nanomaterials, commonly Au, with biomolecules immobilization on their surfaces directly or via various linkers. A variety of surface chemistry approaches on the strength of covalent or non-covalent interactions were utilized to modify...
FIGURE 7  (A) Schematic illustration of biomolecule immobilization on Au nanostructures for LSPR biosensing. (B) Scheme of the simplified measurement setup. (C) Immobilization of anti-hCRP on the surface of Au nanostructures. (D) Specificity analysis of the LSPR sensor. Reproduced with permission. Copyright 2019, Published by American Chemical Society under the terms of Creative Commons Attribution Non-Commercial No Derivative Works (CC-BY-NC-ND) 4.0 license

In consequence, when attaching biomolecules on the surface of metal nanostructures, quantitative assessments of stability and binding efficacy of these approaches are required. Most previous studies were conducted to compare these approaches dealing with spherical nanoparticles or thin film configurations, and few were known regarding attachment of biomolecules on the surface of plasmonic metal nanostructures with other morphologies.

Previous comparison of fabrication strategies on the surface of spherical Au nanostructures has demonstrated that physical absorption led to the higher doses of immobilized antibodies compared to that using other immobilization methods. Several surface chemistry-based approaches for biomolecules immobilization on the surface of nonspherical Au nanostructures were compared and the influence of nonspherical shapes of Au nanostructure on the performance of LSPR biosensing was then assessed. When nonspherical Au nanostructures were utilized to perform LSPR sensing, protein binding via an 11-mercaptoundecanoic acid linker gained reproducible and the most efficient antibody immobilization (Figures 7A and 7B). Furthermore, immobilized antibodies maintained high stability and specificity toward human C-reactive protein (hCRP) via an immunoassay using diluted hCRP-spiked human serum samples (Figure 7C). The limits of detection and limits of quantification of this sensor were determined to be 41.0 and 124.2 ng/mL, respectively (Figure 7D). Therefore, this work revealed crucial information regarding effective immobilization of biomolecules for plasmonic biosensing to achieve more sensitive detection and more accurate diagnostics.

4  |  MATERDICINE IN THERAPEUTIC APPLICATIONS

In the past decades, numerous advanced imaging techniques, such as MRI, PET, and CT, have been elaborately allied with a variety of biocompatible nanomaterials to establish various intelligent nanoplatforms for precision
Photodynamic therapy

Noninvasive PDT has become an attractive therapeutic strategy for local treatment of a variety of cancers in clinic, including skin cancers, non-small cell lung cancers, and esophageal cancers. Generally, photosensitizers are initially accumulated at diseased sites and then activated by light with a specific wavelength to generate reactive oxygen species (ROS), leading to cancer cell death via the oxidation of lipids, protein, DNA, and RNA. Owing to the spatiotemporal modulation of light irradiation, ROS can be only produced at tumor tissues rather than surrounding healthy tissues, so as to achieve tumor-specific PDT with negligible adverse effect. Upon excitation by light at a specific wavelength, a photosensitizer tends to be activated to its excited triplet state, which undergoes two reaction pathways. For type I PDT, the excited photosensitizer reacts directly with the biological constituents to generate highly reactive superoxide anions \( \text{(O}_2^-\text{)} \) or peroxides \( \text{(O}_2^{2-}\text{)} \). Alternatively, the photosensitizer at the triplet state can transfer the energy to oxygen to form single oxygen \( \text{(O}_2\text{)} \) for type II PDT. Most organic photosensitizers (eg, porphyrin, chlorin, and phthalocyanine) are engaged in the type II PDT with oxygen supply for \( \text{O}_2 \) production, which only works in well-oxygenated circumstances and thus compromises the therapeutic efficacy in treating oxygen-deficient tumors. However, some inorganic photosensitizers, such as TiO\(_2\), CdS, and \( \text{W}_{18}\text{O}_{49} \), can be activated to generate \( \bullet\text{OH} \) through type I PDT process, which remains effective in oxygen-deficient tumor microenvironment. Owing to the favorable feature of oxygen irrelevance for type I photochemical reaction process, extensive endeavors have been devoted to exploring high-performance photosensitizers to effectively treat hypoxic tumors.

The widely used photosensitizers tend to form aggregation in aqueous solution due to their hydrophobic feature and rigid planar structures. Aggregation in biological environment, quenched fluorescence, and decreased ROS production significantly lower the PDT efficacy of most photosensitizers. Moreover, the further application of PDT in clinic is severely hampered by other factors, including oxygen-deficient microenvironment in tumor tissues and intrinsic oxidative resistance. To solve this problem, the carrier-free hybrid nanospheres were rationally engineered through coordination-driven self-assembly of an aggregation-induced emission photosensitizer (TPEDCC), ferric ions (Fe\(^{3+}\)), and a B-cell lymphoma 2 (Bcl-2) inhibitor (sabutoclax) for imaging-guided and enhanced PDT (Figure 8A). After internalization by tumor cells, Fe\(^{3+}\) reacted with \( \text{H}_2\text{O}_2 \) through Fenton reaction to relieve tumor hypoxia. Meanwhile, in vivo PDT resistance of TPEDCC was alleviated by sustained release of sabutoclax. Importantly, the hybrid nanospheres presented intense fluorescence with high ROS production efficiency upon laser irradiation, making them the fantastic candidates for augmented PDT under the guidance...
FIGURE 8  (A) Schematic representation of the fabrication of hybrid nanospheres and Fenton reaction-enhanced PDT. (B) Confocal imaging of intracellular ROS generation after various treatments. (C) Cellular viability of MDA-MB-231 cells after incubation with various nanoformulations. (D) In vivo fluorescence imaging, and (E) biodistribution profile of MDA-MB-231 tumor-bearing mice after intravenous administration of hybrid nanospheres. (F) Tumor-volume curves in various treatment groups. Reproduced with permission. Copyright 2020, American Chemical Society
of optical imaging (Figures 8B and 8C). Compared with other treatment groups, the nanospheres exhibited higher cytotoxicity toward MDA-MB-231 breast cancer cells with an IC\textsubscript{50} value of 4.67 \(\mu\)M upon 410 nm laser irradiation, whereas an improved PDT efficiency could not be detected in normal 3T3 cells due to the low expression level of Bcl-2 in 3T3 cells (Figure 8D). In vivo fluorescence imaging displayed that the fluorescence signal of nanospheres at tumor sites achieved the maximum at 4 h postinjection (Figure 8E). More importantly, the best therapeutic efficacy in vivo was evidenced with nanosphere incubation plus laser irradiation, where Bcl expression was apparently declined and tumor growth was almost completely suppressed (Figure 8F). Although the multifunctional hybrid nanospheres presented a prospective nanoplatform for optical bioimaging-guided and augmented PDT, limited penetration depth of 410-nm laser hampered the further application of the designed nanospheres.

### 4.2 Photothermal therapy

The past decade has undergone explosive development in the implementation of photonic hyperthermia for thermal ablation of malignant tumors. In PTT process, photothermal conversion agents are first delivered to tumor sites through intravenous or intratumoral injection. Subsequent exposure of the tumors to NIR lasers induces synchronized oscillation of conduction band electrons of photothermal agents, which thus leads to hyperthermia effects. The heating effects can elevate the tumor temperature to induce irreversible cellular damage and significant tumor suppression.\textsuperscript{109} Currently, a large amount of biomaterials have been exploited as effective PTT agents for photonic hyperthermia, such as organic NIR dye,\textsuperscript{110} inorganic materials,\textsuperscript{111} and polymer nanoparticles.\textsuperscript{112} Despite their prominent PTT efficacy, most PTT agents in the NIR-I biowindow have been comprehensively investigated in animal models. Recently, photothermal conversion in the NIR-II biowindow, particularly within 1000-1100 nm, has aroused growing concern because it allows deeper penetration depth in tumor tissues, lower background signal, and higher maximum permissible exposure compared to that in NIR-I biowindow.\textsuperscript{113} However, only a few paradigms of NIR-II-absorbing PTT materials, including noble metal materials (Figure 9A),\textsuperscript{113c} ammonium tungsten bronze nanoparticles (Figure 9B),\textsuperscript{114} two-dimensional MXenes (Figure 9C),\textsuperscript{115} copper sulfide (CuS) nanoparticles,\textsuperscript{116} and large conjugated polymer nanoparticles (Figure 9D),\textsuperscript{112a} have been successfully demonstrated for in vivo applications.

### 4.3 US-based therapy

The biomedical use of US has evolved from the clinic application as a bioimaging tool to an expanding field of therapeutic capability for cancer treatment.\textsuperscript{117} The energy
deposited originating from the focused US waves can translate into the heating effects for tumor ablation, resulting in high-intensity focused ultrasound thermal ablation, which can serve as an adjuvant therapeutic modality for traditional cancer therapy.\(^{118}\) Alternatively, a less exploited but more attractive therapeutic use of lower intensity US is the acoustic activation of sonosensitizers, termed as sonodynamic therapy, which yields localized cytotoxicity attributing to the efficient ROS generation.\(^{119}\) Capitalizing on the deep-tissue penetration capability of US, SDT has thereby emerged as a potential alternative to PDT for treating tumors located at deep tissues, whereas it still possess its strengths over conventional therapeutic strategies, including minimal invasiveness, high precision, and desirable biocompatibility.\(^{120}\)

The hydrophobic property of most organic sonosensitizers, such as protoporphyrin IX (PpIX), hematoporphyrin, and phthalocyanine, reduces their bioavailability and therapeutic dose in vivo.\(^{121}\) Nevertheless, assembling free organic sonosensitizers within nanostructures can circumvent this challenge, enabling high concentration of sonosensitizers to accumulate at tumor sites. Moreover, the packing of organic sonosensitizer molecules within a single nanostructure can facilitate more effective SDT via efficient delivery of sonosensitizers to the desired sites.\(^{122}\) For this purpose, high surface area and uniform pore size of hollow mesoporous organosilica nanoparticle (HMONs) rendered dense anchoring of PpIX to achieve augmented SDT efficacy (Figure 10A).\(^{123}\) After exposure to US stimulation, significant cell elimination in vitro and tumor suppression in vivo was achieved using HMONs-PpIX + US over US exposure alone (Figures 10B and 10C). Despite the sonosensitizer design principles are focused on the utilization of photosensitizers, the application of inorganic nanomaterials in the realm of SDT has provided a new avenue to deliver sensitization for efficient cancer treatment. For instance, titanium oxide (TiO\(_2\)) nanoparticles,\(^{124}\) graphene oxide (GO)-integrated TiO\(_2\) nanoparticles (Figure 10D),\(^{125}\) and Au-deposited TiO\(_2\) nanoparticles (Figure 10E)\(^{126}\) were employed to accelerate electron-hole separation for augmented SDT by amplifying ROS generation.

### 4.4 Magnetic hyperthermia therapy

Because of the intrinsic superparamagnetic features, Fe\(_3\)O\(_4\) nanoparticles can efficiently accumulate in tumor tissues and generate heat effects to thermally ablate tumors upon exposure to an alternating magnetic field (AMF), which is termed as magnetic hyperthermia therapy.\(^{127}\) Magnetic hyperthermia, featuring noninvasiveness and high selectivity, has been recognized as a

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**FIGURE 10** (A) Schematic illustration of MnPpIX covalently grafted HMONs for SDT. (B) Digital photographs of representative tumors in various treatment groups. (C) Tumor-volume variations after various treatments. (A–C) Reproduced with permission.\(^ {123}\) Copyright 2017, American Chemical Society. (D) Scheme of integration of graphene oxide and TiO\(_2\) nanostructures for sonodynamic tumor eradication. Reproduced with permission.\(^ {125}\) Copyright 2017, American Chemical Society. (E) Schematic representation of Au-TiO\(_2\) nanostructures for SDT. Reproduced with permission.\(^ {126}\) Copyright 2016, American Chemical Society.
promising therapeutic modality. In comparison with PTT, MHT can effectively treat deep-seated tumors due to the high tissue penetration capability of AMF. In addition, the remote utilization of AMF renders magnetic hyperthermia to be a controllable therapeutic modality for eradicating inaccessible tumors and thus minimizing damage effects toward neighboring health tissues.

Despite its high therapeutic potential, MHT only confines to treat localized and readily accessible tumors because tumor temperature can achieve 40°C only through intratumoral administration of Fe₃O₄ nanoparticles. To solve this problem, hexagon-shaped Mn- and Co-doped iron oxide nanoparticles (CoMn-IONP) were rationally designed and synthesized for efficient magnetic hyperthermia (Figure 11A-C). The CoMn-IONP manifested higher saturation magnetization and superior heating efficacy compared to that of Fe₃O₄ nanoparticles (Figures 11D and 11F). Furthermore,
CoMn-IONP efficiently accumulated at tumor sites after intravenous administration (6.0 mg Fe/kg), elevated tumor temperature to 44°C under AMF actuation, and thus substantially suppressed the tumor growth (Figure 11E). To further propel the development of this therapeutic modality, it is crucial to assess the treatment efficacy of magnetic nanoparticles in orthotopic animal models with deep-located tumors in the following studies, which is of high significance for guaranteeing their further clinical translations.

5 | MATERDICINE IN REGENERATION MEDICINE

Numerous diseases, including diabetes, osteoporosis, cardiovascular disease, and cancers, cannot be effectively cured with current clinical treatment approaches due to their limited capability in promoting tissue regeneration. Current treatment strategies aim to replace injured organs and tissues by acquiring tissue from the identical individual or transplantation from cadavers. The ever-growing cases of donor scarcity and organ shortage worldwide are striking warnings of the urgent demand for alternatives to allograft tissues. Regenerative medicine or tissue engineering is a multidisciplinary field that is based on the convergent technologies of materials science, biology, stem cells technology, and clinical translation to regenerate and/or restore damaged tissues as a consequence of disease, congenital abnormalities, or trauma. Engineering functional organs or tissues is a complicated process, which starts with a rational design of scaffold/implant biomaterials. In addition to providing mechanical support, scaffold materials could trigger the release of biochemical signals to promote cell attachment and regulate cellular behaviors, resulting in the assembly of cells into functional units, which is the important components of materdicine. Meanwhile, scaffold materials should possess several characteristics, including suitable macropore structures for nutrients and wastes transportation, excellent biocompatibility with host organs and tissues, and tunable biodegradation capability. Over the past several decades, dozens of fabrication technologies have emerged, covering 3D printing, electrospinning, layer-by-layer assembly techniques, and so forth. The following several paradigms are discussed to reveal the applicability of materdicine in regenerative medicine.

5.1 | Hydrogel

Bone tissue engineering, using biomaterials to deliver the bioactive factors, which can augment the migration of endogenous stem cells to the damaged areas and induce the cellular proliferation and differentiation, has been one of the most prospective strategies for bone tissue regeneration. Biomaterials are adopted to load the bioactive factors for reserving their bioactivity and promoting their sustained release at the defected areas. Among various available biomaterials, polymer hydrogels are the most frequently utilized delivery vehicles for bone regeneration. Nevertheless, the introduction of toxic substances during the synthetic processes limits their further biomedical application. Supramolecular hydrogels, formed through intermolecular interactions (e.g., electrostatic interaction, van der Waals, hydrogen bond, and π-π stacking), are attractive alternatives to polymer hydrogels due to their excellent biocompatibility and biodegradability.

To efficiently accelerate the reconstruction and regeneration of periodontal bone tissues, a biocompatible hydrogelator, NapPhe-Phe-Tyr-OH (NapFFY), was used to co-assemble with stromal cell-derived factor-1 (SDF-1) and bone morphogenetic protein-2 (BMP-2) to fabricate supramolecular hydrogel SDF-1/BMP-2/NapFFY for sustained release of the bioactive factors (Figure 12A). In vitro cumulative release profiles of SDF-1 and BMP-2 from the hydrogel indicated that the bioactive factors could be released in a synchronous sustained manner with the cumulative release rates of 74.8% and 82.1% at 35 day for SDF-1 and BMP-2, respectively (Figure 12B). Critical-sized periodontal bone defect models in rats were treated with the designed hydrogel SDF-1/BMP-2/NapFFY for 8 weeks, illustrating that significantly accelerated bone regeneration was achieved at the defect sites with the bone volume (BV) fraction of 56.7% (Figure 12C). Furthermore, hematoxylin-eosin (H&E) and Masson’s trichrome stainings indicated that compact and thick newborn tissues were found at the bone defect areas in hydrogel-treated group (Figure 12D). It is anticipated that the designed SDF-1/BMP-2/NapFFY hydrogel could act as a prospective alternative of bone transplantation in clinic to repair periodontal bone defects and promote newborn formation.

5.2 | 3D printing scaffolds

3D printing is an innovative and promising fabrication strategy to allow for the appropriate distribution and precise positioning of functional biomaterials, bioactive factors, and heterogeneous cells to create artificial tissue
The quality of the printed scaffolds highly depends on their cellular response, exposed tissue microenvironment, biodegradability, and biocompatibility. Furthermore, the large surface area and interconnected pore structure of 3D printing scaffolds can facilitate cellular adhesion, proliferation, intercellular communication, and transplantation of nutrients and wastes.

The treatment approaches for bone cancers in clinic include surgical resection followed with adjuvant chemotherapy or radiation therapy to avoid the remaining of cancer cells and recurrence/metastasis of cancer cells. Although some artificial implants have been utilized in clinic, inferior bone-implant osseointegration and newborn construction difficulty remain a crucial challenge to current surgical strategies. Therefore, it is highly imperative to engineer 3D printing implants with both antineoplastic and bone reconstruction functions. To achieve this goal, a series of 3D printing scaffolds were fabricated and subsequently modified with photothermal conversion agents (eg, graphene oxide, black phosphorous, and polydopamine) for in situ photothermal ablation of tumor cells and bone regeneration. Although satisfactory treatment outcomes have been validated, their treatment performances for tumor ablation and new bone formation were dominantly assessed in separated animal models. Therefore, it is urgently required to establish appropriate practical animal models to evaluate their capability in thermal eradication of tumors and bone regeneration.

An unidentified strategy was presented for bone cancer treatment by rendering a 3D-printing titanium scaffold with anticancer capability through surface engineering scaffolds. The quality of the printed scaffolds highly depends on their cellular response, exposed tissue microenvironment, biodegradability, and biocompatibility. Furthermore, the large surface area and interconnected pore structure of 3D printing scaffolds can facilitate cellular adhesion, proliferation, intercellular communication, and transplantation of nutrients and wastes.

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modification with hydroxyapatite nanoparticles (n-HA, \(\text{[Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\)). In vitro investigations demonstrated that the rod-shaped n-HA caused significant apoptosis in VX2 tumor cells, whereas negligible effect was evidenced in normal L929 cells (Figures 13A and 13B). Moreover, an animal model in immunocompetent rabbits signified that n-HA treatment markedly suppressed tumor growth and prevented lung metastasis, whereas no effect was witnessed in the group treated with titanium dioxide (n-TiO2) or micro-sized HA (\(\mu\)-HA) (Figures 13C and 13D). The mRNA expression profile demonstrated that n-HA substantially upregulated the expression of genes associated with tumor apoptosis via activating the mitochondrial apoptosis pathway (Figure 13E). Furthermore, the potential capability of n-HA-loaded scaffolds in suppressing tumor proliferation, alleviating osteoporosis, and accelerating bone regeneration was confirmed (Figure 13F). Although this study has presented prospective results in suitable animal models, clinical outcomes, including biocompatibility and anticancer efficacy of n-HA, are promising but questions remain, owing to the huge difference between animal disease models and human diseases.

### 5.3 Biomimetic scaffolds

Biomimetic scaffold biomaterials can provide diverse biological, structural, and mechanical cues to promote recruitment, proliferation, and differentiation of mesenchymal stem cells (MSCs) by mimicking the natural bone extracellular matrix (ECM). Synthetic biomimetic scaffolds, which consist of natural collagen and inorganic composites, have aroused considerable attentions owing to
their capability in mimicking the biophysical structure, chemical composition, and mechanical features of natural ECM. Successful biomaterial-mediated bone regeneration relies on complicated host-scaffold interactions including immune response, stem cell attachment, and osteogenic differentiation. The immune response to biomimetic scaffolds is of crucial significance to determining the remodeling of scaffolds and their treatment outcomes in bone regeneration.152

Inspired by the nature design, a bottom-up mineralization strategy was used to fabricate hierarchical intrafibrillarly mineralized collagen (HIMC) with bone-mimicking surface chemistry and nanotopography for endogenous bone regeneration (Figure 14A).153 After implantation of HIMC and NEMC (mineralized collagen without bone-mimicking nanostructure) scaffolds into rat mandible defects, dramatically increased neo-BV was detected in the defect regions in HIMC-treated group at 10 weeks postimplantation, whereas limited neo-bone formation was observed in the defect sites in NEMC-treated group at both 2 and 10 weeks after implantation (Figure 14B-D). H&E staining illustrated that plenty of fibrous bone tissues with blood vessels were observed in the defect areas in the HIMC-treated group, whereas less neo-bone formation was found in the defect sites of both control and NEMC groups (Figures 14E and 14F). The molecular
mechanisms revealed that HIMC facilitated macrophage polarization through interleukin-4 to stimulate osteogenic differentiation of MSCs and thus promote bone regeneration. These findings laid a solid foundation to engineer biomimetic scaffolds for bone tissue reconstruction from an immunomodulation perspective. Despite tremendous progresses have been made using supporting materials (hydrogel, 3D-printing scaffolds, and biomimetic scaffolds) for in vitro cellular proliferation and differentiation as well as in vivo bone regeneration with the objective of achieving efficient therapeutic transplantation, replenishment of dysfunctional organ or tissues in vivo is still in the infancy and exploration stage, attributing to the confined understanding of action mechanisms that modulate tissue homeostasis, healing, and reconstruction. Furthermore, various critical challenges, including insolvency in microenvironment, structural stability, the degradation rates of support scaffolds congruent with the tissue regeneration rates, and nontoxic property, need to be addressed for further clinical translation.

6 | BIOCOMPATIBILITY AND BIOSAFETY OF BIOMATERIALS IN MATERDICINE

The clinical translation of versatile biomaterials in materdicine strongly depends on their biocompatibility and biosafety, which requires the strict evaluation and assessment to provide the solid evidence. Because of the abundant composition and structures of diverse biomaterials, it is highly complex and challenging to acquire the regular data that are applicable to all biomaterials. Herein, we only focus on and discuss the biocompatibility and biosafety of nanoscale biomaterials to clarify the importance and possible strategies to assess the biosafety and biological effects of biomaterials in materdicine. Benefiting from the unique physiochemical features, including optical, magnetic, thermal, redox properties, and catalytic performance, a large amount of nanomaterials as versatile nanoplatforms revealed tremendous potential in the diagnosis and treatment of diseases, such as imaging, drug delivery, tissue repair, controlled release of free radicals, and thermal eradication. Despite the remarkable progresses have been achieved over the past decades, it is also worth considering the possible safety risks related to their interactions with biological defense systems in living organisms. Typically, once delivered into the body for diagnostic or therapeutic intent, nanomaterials should implement their expected functions and be excreted from the body with high biosafety. Actually, a wide range of research studies have demonstrated that numerous nanomaterials manifest minor to major toxic effects. Therefore, it is essential to comprehensively assess various nanomaterials from the toxicological perspective to determine safe working dosage through different administration pathways such as intravenous, subcutaneous, transdermal, intraperitoneal inhalation, and oral administrations.

Despite systematical investigations have been conducted to comprehend and evaluate toxic effects of diverse nanomaterials on biological systems, clinical trials of the most nanomaterials in humans have not been performed and realized, hindering the further translation applications, which is because our comprehension of the full extent of biocompatibility/biosafety of nanomaterials in a variety of biological systems is still far from sufficient. This fact is attributed to the biological effects of these nanomaterials that are extremely complicated as they primarily depend on a succession of unique features of nanomaterials, such as particle size, shape, composition, surface chemistry, as well as the synthetic approaches. For instance, after systemic administration, nanoparticles can be identified by the biological immune systems as foreign materials and then trapped by the RES, such as spleen and liver, resulting in long-term retention and potential toxic effects on the host. The severity of adverse effects depends on the type of host-guest interactions and the administration dosage. Physical and chemical parameters (eg, size, shape, surface chemistry, and chemical composition) of nanomaterials and immunological interactions mainly affect the biocompatibility and other biological behaviors (eg, biodistribution, biodegradation, and metabolism) of nanomaterials inside the body via their respective toxicological mechanisms.

6.1 | Nanoparticle dimensions

The ratio of surface area and volume of nanoparticles increases exponentially with the diminishing of particle size. Such “quantum size effect” causes intricate interactions between biomolecules (eg, protein, DNA, and peptide) and nanomaterials and thus determines several attributes of nanomaterials in the biological environment, playing a crucial role in toxic effects. Attributes include their tendency to escape from immune surveillance, promote body circulation, infiltrate various organs and tissues, pass through biological barriers, and eliminate from the body. It has been demonstrated that nanomaterials less than 5.5 nm can be eliminated from the body though renal filtration pathway. However, rapid clearance of nanomaterials leads to reduced circulation duration in vivo and thus shortens their available time to implement their desired functions. In contrast, nanomaterials with large size ranging from 20 to 200 nm not only feature...
prolonged residence time in the body but also offer more opportunities to achieve their multifunctionality via modifying targeting ligands and loading drugs. However, large-sized nanoparticles are inclined to accumulate in RES, leading to potential toxic effects on biological system. Therefore, one promising strategy is to engineer degradable nanoplatforms and nanoplatforms of appropriate size, which allow their sufficient time to perform the expected functions, and can also be decomposed into small-sized degradation products that can be rapidly cleared from the body.

6.2 | Morphology

The interactions of nanomaterials with proteins significantly influence their biological effects both in vitro and in vivo. The biological interface formed by proteins absorption promotes their internalization into cells via receptor-mediated endocytosis. Nonspecific protein absorption by nanoparticles causes rapid clearance from the RES, inducing endocytosis through interaction with cell membranes, thus causing cytotoxicity.

The shapes (eg, spheres, filaments, ellipsoids, cylinders, and planar surfaces) of nanomaterials play a critical role in evoking toxicity during the processes of surface interaction with the cellular structure.

Some investigations have demonstrated that the high aspect ratio of materials results in the pore formation in the cell membrane, which thus causes destruction of ionic aggregation along the cellular membrane. For instance, after intraperitoneal injection of carbon nanotubes with various lengths into female C57BL/6 mice, histological diaphragms revealed granulomatous inflammation. However, other investigations demonstrated that no palpable systemic toxicity was caused by intravenous injection of high aspect ratio of carbon nanotubes, and the toxicity could be relieved through appropriate modification with PEG/phospholipid. Encouraged by the mechanism that flexible polymer ligands could mitigate nonspecific protein absorption, transformable ultrathin Gd₂O₃ nanocoils remarkably reduced nonspecific protein adsorption to hamper cellular internalization. After intravenous injection of the nanocoils, the transformable nanocoils presented a shedding nature to circumvent rapid clearance and lengthen their circulation time.

6.3 | Surface chemistry

Surface chemistry of nanomaterials is one of the crucial factors that regulates their biological behaviors in the physiological environments. The biological behaviors of nanomaterials, including biochemical reactivity, aggregation tendency, biodistribution, pharmacodynamics, cell internalization and intracellular distribution, biodegradability, and excretion, exhibit direct influence on their toxicological profiles. Reducing the size of nanomaterials down to nanoscale would increase the number of crystal lattice defects and atoms on the surface of nanomaterials and thus improve their surface energy and biochemical reactivity. The high surface energy of nanomaterials can be liberated through the generation of free radicals, such as ROS, which leads to damage effects on important biological macromolecules (eg, DNA, protein, and lipid). In addition, the disintegration of toxic ions from the surface of nanomaterials, such as Cd²⁺, Zn²⁺, and Ag⁺, also causes severe cellular dysfunction and organelle damage. Nonetheless, the ROS generation and the leakage of toxic ions largely rely on the composition of nanoparticles. Thus, to circumvent the potential toxicity of nanomaterials, the surface reactivity should be “quenched” by surface modification with various molecules (eg, surface ligands, lipids, and polymers) via noncovalent or covalent interactions.

Furthermore, the charged free reactive moieties, such as amines (cationic), carboxylic acids (anionic), sulfonic acids (anionic), and proteins (zwitterionic), on the surface of nanomaterials play a critical role in evoking toxicity during the processes of surface interaction with the cellular structure.

6.4 | Chemical composition

The biodegradable behaviors of biomaterials significantly affect their biosafety through reacting with endogenous substances via chemical or enzymatic reactions to decompose into tiny fragments facilitating rapid excretion from the body. In the past decades, biodegradable biomaterials, such as SiO₂ nanoparticles, MnO₂ nanoparticles, Fe₃O₄ nanoparticles, and transition metal dichalcogenide nanoparticles, have been extensively investigated for biomedical applications. For example, MnO₂
TABLE 1  The selected paradigms of biomaterials for versatile biomedical applications

| Biomaterials          | Biomedical applications | Biomedical performance                                                                 | Reference |
|-----------------------|-------------------------|----------------------------------------------------------------------------------------|-----------|
| USIONCs               | MRI                     | Prominent capability in T1 MRI contrast enhancement                                      | 41        |
| RIAs                  | MRI                     | Highly sensitive diagnosis of HCC                                                       | 43        |
| Tm^{3+}-sensitized NaYF_{4}:Tm^{3+}/Er^{3+}@NaYF_{4} nanocrystals | Optical fluorescence imaging                                                           | Multiplexed encoding and decoding with prominent photostability and high biosecurity | 52        |
| QC nanoparticles      | PA imaging              | Quantitative detection of the expression level of MMP-2 in vivo                         | 59        |
| QD-based NB           | Fluorescent biosensing  | Intracellular nucleic acid labeling and sensing with high sensitivity                   | 70        |
| LUCID                 | Fluorescent biosensing  | Effective detection with high sensitivity, differentiation of bacterial species, and screening of cancer cells | 73        |
| Au nanostructures     | LSPR biosensing         | High stability and specificity toward hCRP                                             | 79        |
| Hybrid nanospheres    | PDT                     | Tumor growth was almost completely suppressed                                           | 108       |
| Au plasmonic blackbodies | PTT                  | Improved PTT outcome of NIR-II over NIR-I                                              | 113c      |
| Ammonium tungsten bronze nanoribbon | PTT       | Advanced CT/PA imaging diagnosis capability                                             | 114       |
| Nb_{2}C nanosheets    | PTT                     | Highly efficient in vivo photothermal ablation and eradication of tumor                 | 115       |
| Cu_{5}S_{4}-Au nanoparticles | PTT               | CT/19F-MRI-guided PTT with negligible background and high penetration depth             | 116       |
| Semiconducting copolymer nanoparticles | PTT       | Superior deep-tissue heating at 1064 nm over that at 808 nm                           | 112a      |
| HMONs-PpIX            | SDT                     | Significant cell elimination in vitro and tumor suppression in vivo                   | 123       |
| Black titania         | SDT                     | Enhanced SDT with high therapeutic biosafety                                          | 124       |
| GO-integrated TiO_{2} nanoparticles | SDT       | Augmenting semiconductor TiO_{2}-based sonocatalytic therapeutic nanomedicine        | 125       |
| Au-TiO_{2} nanocomposite | SDT               | Augmented the levels of ROS generation for cancer therapy                             | 126       |
| CoMn-IONP             | MHT                     | Higher saturation magnetization and superior heating efficacy compared to that of Fe_{3}O_{4} nanoparticles | 131       |
| SDF-1/BMP-2/NapFFY hydrogel | Bone regeneration     | Accelerated bone regeneration was achieved at the defect sites.                        | 145       |
| n-HA                  | Tumor therapy and bone regeneration | Markedly suppressed tumor growth, alleviated osteoporosis, and accelerated bone regeneration. | 150       |
| HIMC                  | Bone regeneration       | Stimulated osteogenic differentiation of MSC and thus promoted bone regeneration        | 153       |

nanoparticles, as common biodegradable nanoagents, contain Mn-O bonds that can specifically decompose into Mn^{2+} in reducing environments. In addition, disulfide bonds were also generally incorporated into some inorganic nanoparticles to endow their biodegradability due to their easy dissociation via glutathione reduction.

Toxicity assessments of micro-/nanoscale biomaterials are of critical significance to their clinic applications. The generally adopted animal models, such as mice, in the field of materdicine may be incapable of capturing the complexity of the biological environment in human beings. Hence, the essential toxicity assessments of biomaterials on nonhuman primates, including biodistribution profiles, excretion, excretion, metabolic byproducts, and long-term toxicity, may provide the valuable information for preclinical use.

7  CONCLUSIONS AND OUTLOOK

Over the past several decades, versatile and functional platforms on the strength of numerous inorganic,
polymeric, and bioinspired biomaterials have been elaborately designed for various aspects of precision medicine.\textsuperscript{75,81} The fast-growing interdisciplinary collaborations between materials science and medical researchers were of crucial importance to the current success in synergistically settling complicated issues in disease diagnosis and treatment. This review aims at presenting a summary and discussion on the use of matericine for disease diagnostic and treatment from a broad perspective. It is noted that the matericine field covers large amounts of biomaterials with abundant functionalities and applications in biomedicine. This review only selected several representative paradigms for clarifying the applicability of matericine (Table 1). First, we present accounts on diverse imaging agents for optical fluorescence imaging, MRI, and PA imaging. In addition, recent advances on biosensing, such as fluorescent and plasmonic sensors, for POC diagnosis are introduced. Moreover, we highlight various therapeutic modalities (PDT, PTT, SDT, and MHT) for achieving enhanced therapeutic efficacy. Furthermore, we summarize the progresses of scaffold materials (hydrogel, 3D printing scaffolds, and biomimetic scaffolds) for regenerative medicine. Additionally, the chemical control of toxicity of materials (dimensions, morphology, surface chemistry, and chemical composition) is also discussed to address the toxicity issues. Despite the field of matericine is undergoing explosive growth in each branch and provides a variety of opportunities for disease diagnosis and treatment in a safer and more effective manner, there still remain several critical challenges for clinical translation (Figure 15).

1. Precise manufacturing and large-scale production of biomaterials: A crucial factor of successful translation of biomaterials is the capability to precisely manufacture them for translational use and retain their physicochemical features, including shape, size, surface charge, and compositions. The fabrication reproducibility issues should be carefully addressed for guaranteeing the following theranostic performance. To surmount this challenge, the standardized fabrication approaches should be explored to control the synthetic procedure of diverse biomaterials. Additionally, scaling-up production at a competitive cost is the main challenge to be addressed to move into industrial translation and clinical stages.

2. Choosing appropriate preclinical models: Typically, the animal models cannot actually mimic the practical condition in human body. For instance, the mostly employed xenograft models may reveal inaccurate accumulation levels of nanoparticles by the typical EPR effect, thus providing false information for preclinical studies. It is worth noting that the choice of preclinical animal models significantly determines the distribution profiles of biomaterials within the body. In addition, it has been demonstrated that the clearance of nanoparticles differs across diverse animal species. For instance, humans, monkeys, rats, rabbits, and mice exhibit pri-
mary uptake of large-sized nanoparticles in their livers, whereas high levels of the identical nanoparticles accumulate in the lungs of animal models, such as sheep, pigs, cats, and goats. Therefore, it is highly urgent and necessary to choose proper preclinical models to validate the theranostic performance of biomaterials in materdicine, covering the adoption of positive/negative cell lines, proper animal models, and standard therapeutic approaches.

3. Integration of diagnosis and treatment: One of the biggest targets of nanomaterials in biomedical application lies in the possibility of achieving the integration of diagnosis and treatment by a single nanoformulation. However, few promising paradigms that can facilitate precise and real-time monitoring of treatment actions have been demonstrated. Successful disease treatment could not be achieved without precise disease diagnosis. The real-time and multimodal imaging monitoring provides accurate information for disease location, thus enabling subsequent efficient disease treatment. For instance, exploring theranostic materials for “see&treat” action is intriguing, as it is of crucial importance to a patient who needs not to wait for post-treatment assessments to ascertain the therapeutic outcome. Furthermore, to address the therapeutic purposes appropriately, biomaterials should be rationally designed that take the pharmacokinetics and pharmacodynamics properties into consideration to develop an optimal cancer treatment. By acquiring these capabilities, one can anticipate the emergence of precision anticancer therapy, with which the significant variations of cancers can be addressed in given patients. Additionally, this requires in-depth comprehension of the mechanisms of cancer development and biomaterials requirements for current clinical theranostic modalities.

4. Development of novel cell molecular assays: Further endeavors are required in the fields of novel scaffold biomaterials, novel biological receptors, and the design of novel biosensing concept that can adopt emerging and existing bioimaging modalities. Innovations in developing stable biological receptors for long-term monitoring will also provide an avenue for sensing new analytes. Novel single-cell molecular biosensing using Raman molecular probes may be of crucial importance to the development of precision and personalized medicine.

5. Understanding the underlying mechanisms of action involved in regenerative medicine: Despite the experience acquired from the clinic can lead to the discovery of new regenerative materials or drugs together with crucial mechanisms of treatment action involved, the exploration of desirable candidate biomaterials requires a comprehensive understanding of the underlying cellular targets and signaling pathways associated with their pharmacological behaviors. In addition, the critical challenges in regenerative medicine, including the clinical translation to humans, definitely need to be urgently addressed.

6. Toxicity assessments of biomaterials in materdicine: The potential toxicity of biomaterials is one of the critical barriers to their practical applications in medicine. Hence, the comprehensive evaluation of the biocompatibility and biosafety of biomaterials both in vitro and in vivo is crucial to their clinical translation and use. For in vivo assessment, relevant circumstances in clinic need to be assessed, which involve considerations such as dosage regimens, biodistribution profiles, excretion, metabolic byproducts, as well as acute and long-term toxicity. Moreover, frequently adopted animal models such as mice in biomedical evaluations may be incapable of capturing the complicated in vivo microenvironment in humans. In consequence, it is essential to implement toxicity evaluation of biomaterials on large animals or even nonhuman primates to provide valuable clues for their potential translational use.

Despite there still remain a diverse array of critical issues that require to be urgently addressed, it is highly anticipated that the emerging materdicine can revolutionize the clinical medicine on diagnosis and treatment of various diseases, which requires the convergence and collaboration of researchers and scientists from multiple disciplines with varied backgrounds, working together to promote the progresses of materdicine for benefiting the health of human beings.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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