MINI-REVIEW

Cutting-edge advancements of nanomaterials for medi-translatable noninvasive theranostic modalities

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Abstract
Disease-oriented theranostic modalities have witnessed rapid developments in the past decade, and some of them are on the road of medi-translation for successful clinical utilities. Thanks to their unprecedented convenience, minimized side-effect, satisfactory prognosis, and good controllability by external sources such as light, sound, electricity, heat and magnetism, recent advancements on noninvasive theranostic modalities have opened up a new window for the dawn and light-shedding of cutting-edge functional nanomaterials in association with current commercialized clinical devices to serve precision and visualized medicine for new-generation disease-oriented healthcare resolutions. This review summarizes the latest progresses on the advanced nanomaterial developments as well as their emerging applications to image-based diagnosis and noninvasive treatments by external stimuli sources. Furthermore, their state-of-the-art biomedical translations have been highlighted to outlook the prevailing trends for clinical uses, and current challenges are discussed for sake of comprehensive safety issues before to humans.

KEYWORDS
medical translation, nanomedicine, noninvasive modality, photodynamic therapy, photothermal treatment

1 | INTRODUCTION

Various disease-oriented theranostic modalities have been developed in the past decade, and nowadays they are widely applied pre-clinically or on their way for clinical translations.1,2 In particular, noninvasive methodology on biomedical diagnosis and treatment provides unprecedented convenience, minimized side-effect, satisfactory prognosis, and good controllability by external sources such as light, sound, electricity, heat, and magnetism.3−5 Compared to traditional invasive approaches, e.g. radio- or chemotherapy and surgery, advanced noninvasive modalities have exerted prominent advantages and availability in association with current commercialized clinical devices (Table 1). Besides that, precision medicine in a visualized manner (or called visualized medicine) always requires advanced noninvasive or minimally invasive approaches to serve the discrimination of diseased tissues...
TABLE 1  Representative noninvasive theranostic modalities against various diseases

| Noninvasive theranostic modalities | Advanced therapy                  |
|-----------------------------------|-----------------------------------|
| Image-based diagnosis             | Advanced therapy                  |
| Photoacoustic imaging (PAI)       | Ref. 8–16                         |
| Ultrasonography (US)              | Ref. 17                           |
| Magneto-acoustic imaging (MAI)    | Ref. 18                           |
| Magnetic resonance imaging (MRI)  | Ref. 19                           |
| Optical imaging (OI)              | Ref. 20,21                        |
| Multimodality imaging             | Multimodality therapy             |

Advanced therapy

Noninvasive Theranostic Modalities on Biomedical Translations

2.1 Noninvasive disease-oriented diagnostic modality

Biomedical imaging is capable to provide sufficient pathological information prior to surgery to afford major arena among non-invasive biomedical theranostic modalities that can help accurate diagnosis. High-resolution anatomical and functional images are rational treatment plans and can also evaluate the treatment efficiency and recovery status post-surgery in a real-time manner. Compared with single modality imaging, the brand-new multimodality molecular imaging exhibits unique merits which not only enhance our better understanding on pathogenesis and characteristics of disease developments and metastasis at the molecular or cellular level, but also detect the variation and pathology phenomena at an early stage. Our group has developed functional contrast agents based on the multimodality imaging of ultrasound, fluorescence imaging, and MRI to track the reticuloendothelial cells in vivo, probe the tumor lesions, and facilitate the pre-treatment image guidance.

Photoacoustic imaging owns the high sensitivity and acceptable deep penetration into tissues, and it has become a powerful modality for detecting superficial malignant lesions (such as breast cancer and melanoma) or combines with endoscopy. Carbon dots (CDs) have attracted much attention because of their excellent properties such as chemical inertness, colloidal stability, easy functionalization and excellent biocompatibility, and various carbon source materials (such as milk, soybean soap, honey, and glucose) have been used as green sources to produce CDs. We embedded methylene blue (MB) as a fluorescent dye into CDs, and the composite nanoprobes were synthesized by a one-pot microwaving protocol to fabricate MB-embedded nanocomposites (MB-CDs) for in vivo photoacoustic imaging in live mice eyes (Figures 2A-2D).8
The successful loading of MB prevented rapid clearance out of the body, and in the meanwhile enhanced their biocompatibility. A novel multi-mode cell trafficking was realized by using these composite CDs as nanoprobes to trace ocular blood vessels. While these MB-CDs were intravenously injected into nude mice, the blood circulation pumped them into eyes with the photoacoustic imaging signals were recorded (Figures 2E and 2F). By deducting the intrinsic photoacoustic signals from hemoglobin (Hb), these images showed signals from MB-CDs trapped in the reticuloendothelial cells, which clearly displayed the lesions. Thus, this was the first report using MB-CDs to image reticuloendothelial cells in live mice by the modality of photoacoustic imaging, and this paved the way to detect
the pathological damage or dysfunctions on ocular blood vessels or capillaries in live animals.

Pu built poly(N,N-dimethylacrylamide)-r-(hydroxypropyl acrylate) grafted semi-conducting polymers (SPNph1) as a thermo-responsive PA agent to enhance the contrast of vivo imaging. SPNph1 possessed higher thermo-responsive PA property, higher PA intensity, stronger PA signal, and higher-contrast tumor imaging. The inherent optical absorbance of biomolecules (e.g., Hb, melanin, etc.) often shows background tissue signals to interfere with signals from the contrast agents during in vivo PAI. Liu designed a unique US-responsive photonic microbubbles (MBs) for in vivo background-free PAI. It could also promote the next-generation US/PA dual-model imaging agents which was particularly promising for the accurate PA detection of targets in organs with complicated blood vessels (Figure 3).10

Photoacoustic imaging is a non-destructive biophotonic imaging method based on ultrasound absorption differences in biological tissues. It combines the advantages of high refractive index characteristics of pure optical imaging and high penetration depth characteristics of pure ultrasound imaging. The detector detects photoacoustic waves instead of photon in optical imaging, avoiding the effect of optical scattering in principle. It can provide tissue imaging for high-beam and transmitted, and also can provide an important means for studying the structural shape, physiological characteristics, metabolic function, and pathological characteristics. Therefore, photoacoustic imaging has broad applications in biomedical diagnosis, especially body tissue structure and functional imaging.

Chen developed an intelligent PA probe that can self-assemble and regenerate for use in reactive oxygen species (ROS) targets in live animals to enhance PA imaging. The probe consists of a phthalocyanine core with near-infrared (NIR) absorption and polyethylene glycol (PEG) arms connected by ROS-reactive self-eliminating segments. This structure keeps probe stable in aqueous solution, but after ROS-induced PEG cleavage, it self-assembled and re-grew into large nanoparticles, releasing hydrophilic PEG and enhancing the hydrophobicity. Thus, the residual phthalocyanine grew into large-sized nanoparticles, resulting in the enhanced ROS PA signal. The small size intact molecular probe facilitates penetration into the tumor tissue of live mice, and the regrowth of ROS-activated nanoparticles prolongs the retention time, while enhancing the PA signal, thereby allowing ROS to be imaged during chemotherapy. Therefore, this probe design method can also be a commonly important targets to detect other physiologically data. A type of semi-conductor polymer nanoparticles as NIR-II PA agents with high in vivo clearance was reported.12 The completely organic nano-agent included the oxidizable optical polymer as a PA generator and the hydrolyzable amphiphilic polymer as a particle matrix to provide water solubility. In particular, these agents possessed high photothermal conversion efficiency and non-toxic in vivo.

In order to in vivo optically image drug-induced acute kidney injury (AKI), the molecular renal probes (MRPs) with high renal clearance efficiency were developed.13 This probe represents almost completely clearance via the kidney, specifically reacts with the targeted biomarkers, and spontaneously activates its optical signals, which is abnormal upregulation before the decrease in MRPs at the incipient stage of drug induced AKI. This active imaging mechanism enables MRPs to noninvasively detect the onset of

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**FIGURE 3** Schematic illustration of ultrasound-responsive conversion of microbubbles to nanoparticles. (Reproduced from Liu et al, ultrasound-responsive conversion of microbubbles to nanoparticles to enable background-free in vivo photoacoustic imaging, Nano Lett, 2019, 19, 8109 with the permission of American Chemical Society.)
AKI induced by cisplatin at least 36 hours earlier than the existing imaging methods.

In order to enhance multimodal imaging-guided cancer treatment, Li et al fabricated organic multimodal photothermal nano-agents that can biomimetically target cancer-related fibroblasts in tumor microenvironment (TME). Such bionic nano-camouflage included SPN that absorb near infrared, which are covered by cell membranes of activated fibroblasts. The homologous targeting mechanism of SPN preferentially targeted the cancer-related fibroblasts (AF). Because of the homogenous targeting capability, AF-SPN treated cells were 3.9- and 2.5-fold higher than uSPN and CC-SPN treated cells in the mean fluorescence intensity. AF-SPN provides stronger NIR fluorescence and photoacoustic signals to detect tumors and produces enhanced cytotoxic heat and singlet oxygen (Figure 4). Therefore, the combination of photothermal and photodynamic therapy will ultimately have higher antitumor efficacy than other ordinary drugs.

Integrin $\alpha_v\beta_3$ family has great influence in the process of tumor neovascularization, development, and metastasis. They are usually overexpressed in tumor cell membrane and endothelial cells, which can be used as tumor targeting markers. With the covalent bio-conjugation of RGD peptides on the surface of MB-CDs, these nanoprobes (MB-CDs@NH-RGD) could be used to specifically target the tumor cells of breast cancer (MDA-MB231) and melanoma (B16) via the selective binding between RGD sequences and integrin $\alpha_v\beta_3$ receptors that were overexpressed on the cell membrane (Figure 5A). Interestingly, significant photothermal effect was found when these agents were exposed to an NIR laser of 808 nm (Figure 5B), which indicated their potential utility as multifunctional agents for thermal ablation in vivo. Furthermore, resulted from the optical features of CDs, these agents were utilized for cell labeling and were visualized via a dual-channel (wavelength: 405 nm and 640 nm) under a confocal laser scanning microscopy, which further improved the accuracy of cell tracing and lesion orientation (Figures 5C and 5D). With the intravenous injection into the MDA-MB231 tumor-xenografted nude mice, time-dependent specific accumulation of MB-CDs@NH-RGD at the tumor lesion was observed, and the photoacoustic signal intensity also increased consequently to precisely visualize the tumor lesion margin.

In addition to integrin $\alpha_v\beta_3$ family, folic acid (FA) is another representative biomarker used for high-specificity tumor targeting. Our group synthesized hybrid polymeric MB-embedded nanoprobes (poly butyl cyanoacrylate [PBCA]-MB@CS-FA) for folate receptor-targeted photoacoustic imaging in vivo. The photoacoustic signal intensity reached 10 times higher than those of non-targeted control groups. Therefore, it is valuable for early-stage noninvasive diagnosis before treatment guidance of breast cancers.

Gas-filled MBs are common contrast agents used for ultrasound imaging to achieve the contrast enhancement because of the acoustic impedance between MBs and surrounded tissues. Based on the shell material composition, MBs can be generally divided into two types: (lipid-based) soft-shelled and (polymer- or protein-based) hard-shelled MBs. Our group prepared the polymeric hard-shelled MBs
The fabrication of integrin $\alpha_v\beta_3$ targeted nanoprobes (MB-CDs@NH-RGD) (A) their photothermal effect when irradiated with an 808 nm NIR laser (B) and biomedical applications for dual-channel cell labeling to tumor cells of breast cancer (MDA-MB231) and melanoma (B16) (C and D). (Reproduced from Liu et al, Integrin $\alpha_v\beta_3$-targeted C-Dot nanocomposites as multifunctional agents for cell targeting and photoacoustic imaging of superficial malignant tumors, Anal. Chem., 2016, 88, 11955 with the permission of American Chemical Society.)

with PBCA, an FDA-approved biomaterial, which exhibited prolonged life-time and excellent stability due to the polymeric shell preventing gas core from shrinkage. With the in situ one-pot polymerization, a narrowly distributed and monodispersed population of MBs could be afforded, and provide a real-time visualization for discriminating versatile processes of molecular imaging, MB disintegration, and drug release from MBs as drug payloads. Thus, it may be used for image-guided surgery and achieve high efficiency of synergistic treatments combining ultrasound and these polymeric MBs.

Ultrasmall superparamagnetic iron oxide nanoparticles (USPIO NPs) are high-sensitivity MRI contrast agents which can afford high spatial resolution and excellent soft tissue contrast. With the encapsulation of USPIO NPs into the MB shell, the magnetic MBs (USPIO-PBCA) were used for MRI-US dual-modality imaging (Figure 6). An enhanced US contrast and increased transverse relaxation rate were achieved, and significant image contrast was observed in the vascularized region of MLS tumors after intravenous injection of USPIO-PBCA MBs.

In addition to magnetic nanoparticles, the bubble shell loads fluorescent dyes or drug molecules when the bubbles are utilized as drug carriers for controllable drug transportation and delivery. Fluorescent magnetic PBCA MBs were synthesized in a one-step approach, and fluorescent dyes or drugs such as Rhodamine B, Nile Red, Coumarin 6, and Doxorubicin could be encapsulated in a high efficiency. These fluorescent MBs can be used as molecular imaging probes for in vivo cell labeling and tracing, and more importantly they are potential functional agents for targeted and stimuli-triggered drug delivery to tumor or inflammation sites. For example, Rhodamine-loaded MBs were used for visualizing and binding angiogenesis and inflammatory endothelium by using a standard fluorescence microscope and a two-photon microscope.

The polymeric MBs can also be used for targeted binding to endothelial cells after the surface conjugation of Arg-Glu-Asp-Val (REDV) as a functional ligand (Figure 7). After chitosan (CS) coating on the MB shell and genipin (GP) cross-linking, fluorescence was introduced which enabled the capability for endothelial cell labeling and early-stage molecular diagnosis to cardiovascular diseases (Figures 7A-7C). As shown in Figure 7D, human vascular endothelial cells (HVECs) were specifically labeled compared to the smooth muscular cells, and active targeting to HVECs has been achieved by a simple modification of polymeric MB by shell CS-GP cross-linking.

Biomedical photonics has become an interdisciplinary and rapidly developing field, and is also an important part of the research in the frontier fields of life science and medical imaging. The multimodal light converters of NIR semiconducting polymer nanoparticles (SPNs) was designed, and the molecular engineering and nanoscale functionalization of SPNs make it a biological photon and a multifunctional biological photonic crystal nanometer platform.
FIGURE 6  Hybrid magnetic microbubbles (USPIO-PBCA) for in vivo dual-modality MRI-US imaging after intravenous injection into an MLS tumor-bearing mouse (arrows indicate the tumor as ROI) (A and C) and US and MRI signal intensity curves before and after microbubble injection (B and D). (Reproduced from Liu et al, Iron oxide nanoparticle-containing microbubble composites as contrast agents for MR and ultrasound dual-modality imaging, Biomaterials, 2011, 32, 6155 with the permission of Elsevier Ltd. 18)

(Figure 8).23 SPNs have promoted the development of biophotonics from ultra-sensitive afterglow imaging and PA imaging activated by deep tissue to photothermal regulation of biomolecular activity and self-regulating phototheranostics.

For example, an afterglow probe activated only in the presence of biothiols, which was used for early detection of drug-induced hepatotoxicity in living mice. Because of their unique afterglow mechanism, SPNs with a diameter of less than 40 nm acted as a simple accumulation agent for tissue imaging, and also as an intelligent activatable probe to report the pathological processes in living animals.24 The afterglow intensity of SPNs is more than 100-fold brighter than inorganic afterglow agents, and the signal is detectable through the body of a live mouse. High-contrast lymph node and tumor imaging in living mice showed that signal-to-noise ratio is 127-times higher than NIR fluorescence imaging.

Pu studied organic semiconducting materials (OSMs) as the optically active components. OSMs, as an imaging agent, have been exploited, transduce biomolecular interactions into secondary NIR fluorescence, chemiluminescence, afterglow or photoacoustic signals, and realize deep-tissue ultrasensitive imaging of biological tissues, disease biomarkers, and physiological indicators.25,26

The positron emission tomography (PET) imaging with quantitative analysis strategies was used to investigate nanoparticle biological behavior in vivo, which provided a new concept for DNA nanotechnology and therapies of various kidney-related diseases, such as AKI. Jiang et al radiolabeled a series of DNA origami nanostructures with Cu-64 to estimate blood tests and kidney tissue staining via PET imaging.27

2.2 Noninvasive advanced treatments for biomedical translations

Irradiated by a NIR light source, photosensitizers that target lesions can generate photo-induced heat, and the local temperature may reach 42°C or even higher, which leads to acute tumor necrosis, apoptosis and fulfills the purpose of tumor inhibition and elimination.28 In this way, photothermal therapy has received considerable attention as a translationable modality for clinical cancer therapy. Liu built an activatable nanozyme-mediated therapeutic reactor for PTT-based image-guidance. In vivo studies showed that activatable nanozyme-mediated 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) ABTS@MIL-100/poly (vinylpyrrolidone) (AMP) nanoreactors (NRs) that open tumors through the
The CS-GP modifications on polymeric microbubble shell for human vascular endothelial cells (HVECs) targeting and labeling in vitro. (Reproduced from Liu et al, Fluorescent genipin cross-linked REDV-conjugated polymeric microbubbles for human vascular endothelial cell (HVEC) targeting, RSC Adv., 2016, 6, 32710 with the permission of Royal Society of Chemistry.)

The nanozyme-mediated “two-step rocket emission-like” process can be specifically activated in the TME. The production of •OH and the clearance of intracellular GSH in the presence of H2O2 reduced the resistance of cancer cells to intracellular oxidative stress and enhanced the chemodynamic therapy (CDT) effect. Besides that, the TME-triggered PTT showed more effective outcome along with minimal non-specific damage.

NaBiF4:Gd@polydopamine@PEG nanomaterials were synthesized with favorable T1-weighted performance to target tumor and localize PTAs. The cell viability was up to 85% while Bi concentration was as high as 800 ppm, which meant that nanomaterials had low cytotoxicity and superior biocompatibility. Meanwhile, it was able to dynamically record the temperature changes in tumors and normal tissues around the tumor, so as to achieve PTT guidance by multi-mode MRI with significant potential in the clinical application (Figure 9).

Meanwhile, based on the tunable photophysical property, chemical flexibility, and good biocompatibility advantages of SPN, iron-chelated semiconducting polycomplex nanoparticles which comprise ferroptosis initiator (Fe3+) and an amphiphilic semiconducting polycomplex were designed. Under the NIR laser irradiation, localized heat was generated, which not only accelerated the Fenton reaction, but also facilitate the PTT treatment. Since the NIR-II light (wavelength: 1000-1300 nm) has a higher maximum permissible energy to skin (1 W cm−2 for 1064 nm, 0.33 W cm−2 for 808 nm) and reduced tissue attenuation, Jiang synthesized the first hybrid semiconducting nanozyme with an enhanced catalytic activity for NIR-II synergistic photothermal...
ferrotherapy to completely eliminate deep-tissue lesions and effectively inhibit cancer remote metastasis. 32

Photodynamic therapy is one of the most important noninvasive modalities, in which photosensitizers are irradiated by a laser source, and ROSs are produced for tumor removal. 33–35 Based on the photodynamic therapy (PDT) fundamentals, it has the characteristics of small trauma, low toxicity, palliative, and synergistic treatment, and thus it become a prevailing noninvasive treatment for various malignant tumors and skin diseases. 36–38 A novel
A nanosystem using a hydrophobic photosensitizer 5,10,15,20-tetrakis(4-methacryloyloxyphenyl)porphyrin (TMPP) with carbon double bonds and a ferrocene-containing amphiphilic block copolymer (PEG-b-PMAEFc) was constructed (Figure 10). The production of singlet oxygen has been greatly enhanced with pH ranges from 6.5 to 7.2 (the environment of normal cells to tumor cells), and the in situ catalytic reaction of tumor cells provided a new opportunity for the development of hydrophobic photosensitizers for PDT.

Sun fabricated a multifunctional up-conversion nanocomposite doped with lanthanide (Ln\textsuperscript{3+}), which not only provided temperature feedback during PTT but also checked out with a PTT-PDT synergistic effect for efficient tumor treatment (Figure 11). Idris et al designed a nano-formulation by using mesoporous SiO\textsubscript{2} as a carrier and up-conversion nanoparticles (UCNPs) as NIR photosensitizers. The UCNPs multicolor emission function of a single excitation wavelength simultaneously activated two photosensitizers to significantly enhance PDT. The in vivo experiments further confirmed that UCNPs injected into the PDT-treated nude mice gave birth to the strong inhibition of tumor growth and proliferation.

To promote the photodynamic process of hypoxic solid tumors, Zhu et al reported hybrid semiconductor nanoparticles by the way of reacting with H\textsubscript{2}O\textsubscript{2} to generate O\textsubscript{2}. In the hypoxic and acidic TME, nano-manganese dioxide flakes are used as sacrificial components to convert H\textsubscript{2}O\textsubscript{2} to O\textsubscript{2}. Nanomedicines have shown success in cancer treatment, but the pharmacological effects of most nanomedicines are usually non-specific to cancer cells because the therapeutic drugs used can induce apoptosis of internal organelles.
Also use semiconductor materials, Pu et al reported a semiconductor photothermal nano-agonist that could specifically initiate cancer cell apoptosis remotely from the cell membrane as an ion channel-targeted nanodrug. When multiple NIR laser irradiations are performed on a time scale of a few seconds, the nano-agonist can repeatedly and locally release cap, thereby multiple activation of TRPV1 channels on the cell membrane.43

PTT and PDT can also be combined with immunotherapy such as immuno-adjuvant and immune checkpoint blockade. The addition of phototherapy greatly enhances vaccination, eliminates secondary or residual tumors, reduces the occurrence of metastasis, and induces long-term immune memory.44 Hou et al designed the antioxidative black phosphorus nanosheets as ROS scavengers to cure AKI in mice, which possessed special optical properties to achieve PTT and PDT.45

Derived from photodynamic therapy, sonosensitizers can also be irradiated by an external ultrasound transducer, and afford ROS for cancer treatments. Since ultrasound has good penetration into deep tissues and may be used with ultrasound cavitation and sonoporation, sonodynamic therapy is regarded as a promising methodology for clinical cancer treatment.46–50 Our group developed a nanocapsule consists of amphiphilic peptides and Rose Bengal (RB) as photo- and sonosensitizers for synergistic cancer treatments with immune enhancement (Figure 12).51 This nanocapsule displayed specific targeting to various superficial malignant tumors such as breast cancers, melanoma, and cervical cancer. The organic dye of RB showed a good encapsulation capacity, and while exposed to an external laser or ultrasound source, it produced considerable ROS which largely improved the tumor inhibition and cell killing capability.

In addition, we also fabricated the self-assembled peptido-nanomicelles and combined PDT, SDT, and chemotherapy for nasopharyngeal carcinoma treatment (Figure 13).52 In vivo mice treatment experiments confirmed their overwhelming tumor prohibition and lesion elimination behavior, and this strategy has provided a promising noninvasive strategy for clinical cancer treatments with wide-scope cancer versatility.
FIGURE 12  The engineered nanocapsules (PARN) self-assembled with a trifunctional peptide of C_{18}GR, RGDS and a difunctional sensitizer (Rose Bengal) (A and B), and their PDT-SDT combinational treatment efficiency (C and D) against SMTs such as melanoma and cervical cancers. (Reproduced from Liu et al, Multifunctional nanocapsules on a seesaw balancing sonodynamic and photodynamic therapies against superficial malignant tumors by effective immune-enhancement, Biomaterials, 2019, 218, 119251 with the permission of Elsevier Ltd.\textsuperscript{51})

FIGURE 13  A schematic illustration of elaborately fabricated RB-loaded peptido-nanomicelles (RBNs) for synergy-enhanced therapy of SDT, PDT and chemotherapy. (Reproduced from Liu et al, Self-assembled peptido-nanomicelles as an engineered formulation for synergy-enhanced combinational SDT, PDT and chemotherapy to nasopharyngeal carcinoma, Chem Commun (Camb), 2019, 55, 10226 with the permission of Royal Society of Chemistry.\textsuperscript{52})
Internalized RGD peptide (iRGD)-modified nanoliposomes were designed for sonodynamic therapy of gliomas under low-intensity focused ultrasound (FUS). Once the blood brain barrier was opened via FUS, presence of iRGD peptide facilitated the targeting to glioma cells with enhanced tumor accumulation and better cancer killing selectivity by in situ generated ROS. Yue et al combined the SDT of nano-ultrasonic sensitizer with immunotherapeutic agent of anti-PD-L1 to prevent the primary tumor growth and detect lung metastasis. This combination treatment also provided long-term immune memory for tumor recurrence after initial tumor elimination. Li et al presented a nano-sonosensitizer formulation-CAT-TCP/FCS nanoparticles, which makes use of the catalase-catalyzed O2 generation from tumor endogenous H2O2 to efficiently relieve hypoxia of tumor tissues via, then improves the therapeutic efficacy of SDT to ablate in situ bladder tumors under ultrasound. Liang et al proposed a new type of Pt-CuS Janus consists of hollow semiconductor CuS as a large internal cavity for sensory molecules in SDT. Due to the local electric field enhancement, the Pt deposition not only enhanced the photothermal performance, but also contributed to a synergistically enhanced SDT-PTT efficiency without significant tumor recurrence.

Zhen et al synthesized a semiconductor polymer nanococktail (SPNCT), which not only converts light energy into heat energy, but also emits temperature-dependent luminescence after stopping light excitation. Because of the elimination of tissue auto-fluorescence, tumors could be detected by this afterglow luminescence of SPNCT more sensitively than fluorescence, and its temperature dependence allows the tumor temperature to be optically monitored under near infrared laser irradiation. Therefore, the representation of the first organic optical nano-system is SPNCT that can perform optical imaging-guided PTT without real-time light excitation.

In situ toxicity of low toxic substances on specific tumor tissues has become a new paradigm in the fight against cancer. Wu et al constructed a hollow mesoporous Prussian blue (HMPB)-based therapeutic nanoplatform, which indicated that drug disulfiram (DSF)@polyvinylpyrrolidone (PVP)/Cu-HMPB realized in situ chemical reaction-activated and DSF hyperthermia-amplified chemotherapy by encapsulating alcohol-abuse DSF into copper-enriched and PVP decorated HMPB nanoparticles. When DSF@PVP/Cu-HMPB is accumulated in tumor, endogenous mild acidity under tumor conditions triggers biodegradation of HMPB nanoparticles, and simultaneously releases DSF and Cu2+. In addition, due to the inherent photothermal conversion effect of PVP/Cu-HMPBs, the hyperthermia produced by near infrared irradiation to lead to enhancing the anticancer effect of DSF, thus inducing apoptosis in vitro and tumor elimination in vivo in both subcutaneous and in situ tumor-bearing models.

Ultrasound-triggered SDT is a non-invasive tumor treatment strategy, and the combination with mild photothermal effect can achieve effective synergistic therapy. Gong et al used the liquid-phase exfoliation to fabricate titanium hydride (TiH1.924) nanodots for effective cancer treatment. The TiH1.924 nanodots not only have highly effective ROS generation capability, but also exhibit strong NIR absorption as photothermal agent. Meanwhile, the PTT-SDT combination therapy provides a new approach for noninvasive tumor treatment by external stimuli.

To realize the synergetic cancer treatment of CDT/starvation/phototherapy/immunotherapy, a multifunctional cascade bioreactor based on hollow mesoporous CuMoS4 (CMS) loaded with glucose oxidase (GOx) was constructed. CMS has superior photothermal conversion efficiency and cytotoxic superoxide anion \( (-\cdot O2^-) \) generation performance under the irradiation of 1064 nm laser, which makes it show remarkable tumor killing ability in phototherapy. Combined with checkpoint blockade therapy, the PEGylated CMS@GOx-based synergistic therapy could stimulate robust immune responses, effectively ablate primary tumor and inhibit tumor metastasis. Ding et al prepared a novel immunoadjuvant by using large-pore mesoporous-silica-coated UCMSs via a typical silica sol–gel reaction. Compared with photodynamic therapy or immunotherapy alone, nanovaccines UCMSs–MC540–TF can effectually restrain tumor growth and improve the survival rate of BALB/c mice bearing colon cancer (CT26), which indicates that UCMSs has higher immunotherapy efficacy and clinical potential for cancer immunotherapy.

3 | OUTLOOK AND PERSPECTIVES

Although the noninvasive theranostic strategies have seen ever-growing developments, the successful clinical translation and actual applications to humans still have to face several issues and obstacles. First of all, the successful combination of these strategies with present clinical devices should be taken into consideration, and this is the prerequisite for them to be used for diagnosis and treatments for human diseases. Either advanced biomaterials or innovated methods should match and be adaptable to the clinical equipment. Secondly, their biosafety, systematic side-effect evaluation, and potential health risks should be pondered. In terms of precision or individualized medicine, no second damage to normal tissues should be induced while the diseased lesions are eliminated. Since the clinical translation of noninvasive
theranostic strategies will be revolutionized to traditional treatments, research scientists, clinicians, and medical rule-makers should work together to constantly improve and push these strategies to standardized protocols and strictly meet the requirements of clinical institutions.

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CONFLICT OF INTEREST
The authors declare that no conflict of interest.

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