Cancer nanotheranostics in the second near-infrared window

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Abstract
Nanotheranostics is an attractive and fast developing nanomedicine technology that integrates both diagnostics and therapeutics in a single nanoplatform. It ensures consistent spatiotemporal distribution and uniform targeting of the imaging and therapeutic agents, thus desirable for real-time monitoring of in situ therapeutic effects and long-term tailorable therapeutics in accordance to disease prognosis for personalized medicine. Optical stimuli of nanotheranostics offer easy and precise controllability to combat cancer. Compared with the conventional use of visible and the first near-infrared region light, using the second near-infrared (NIR-II) region light as the incident excitation enables cancer nanotheranostics to go deeper and with enhanced theranostic efficiency. Realizing the extraordinary advantages of accomplishing cancer nanotheranostics in the NIR-II region, burgeoning research efforts were devoted to this field. This review aims to analyze the available imaging and therapeutic approaches to realize nanotheranostics in the NIR-II region, and to summarize the current applications of cancer nanotheranostics in the NIR-II region. In the end, we will discuss the challenges and outlook on the possible perspectives in the field.

KEYWORDS
cancer, imaging, nanotheranostics, second near-infrared window, therapy

1 | INTRODUCTION
Nanotheranostics is an emerging nanomedicine technology that integrates both diagnostics and therapeutics in a single nanoplatform.1,2 The nanotheranostic platform takes nanomaterials as both diagnostic agents and therapeutic agents, thus ensuring the consistent spatiotemporal distribution and specific targeting of the imaging and therapeutic agents at the disease site, which is difficult to achieve when separately administrating the imaging...
In order to achieve more effective cancer theranostics in the complex biology environment, the property of the incident light to activate the nanoplatform is important. Compared to the conventionally used light excitations in the visible range (400-700 nm) and the first near-infrared (NIR-I) region (700-1000 nm), light in the second near-infrared (NIR-II) region (1000-1700 nm) could bring nanotheranostics to deeper tissue, and with enhanced imaging contrast and less phototoxicity, thus becoming a thriving stimulus for cancer nanotheranostics.\(^5,6\) The working depth of the nanotheranostic platform is determined by the tissue penetration of the incident light. When light propagates in the biological tissue, the scattering and absorption are the main attenuations to stop light from reaching deeper. In the scattering aspect, most types of tissue impose severer scattering to shorter wavelength light compared to longer wavelength light (Figure 1A).\(^3\) In the absorption aspect, because major tissue components (e.g., oxyhemoglobin, deoxyhemoglobin, melanin, and fat) either possess a decreasing light absorption toward the longer wavelength light or exhibit a valley of light absorption in the NIR-II region, the incident light in the NIR-II region is less absorbed by the tissue in the pathway (Figure 1B).\(^5\) As such, incident light in the NIR-II region preserves more energy to activate nanotheranostic platforms in vivo compared to that of the shorter wavelength light in the visible or NIR-I region, especially for the deep tissue applications. In addition, the less scattered and absorbed NIR-II light enables enhanced imaging ability of the nanotheranostic platform. This is because, when using visible or NIR-I light as the excitation, the nonfocused and random directional scattering light usually imposes severe background noise to the imaging signal, thus undermining the imaging quality. Moreover, the weak absorption of NIR-II light also avoids autofluorescence interference from the biological sample, which is often the case using visible light as the excitation.\(^7\) Thus, NIR-II light is desirable to improve the imaging quality in cancer nanotheranostics. Since NIR-II light interacts very weakly with biological tissues, their phototoxicity is minimized, which preferably leads to the much-enhanced tolerance of NIR-II light compared to the shorter wavelength light in biological tissue. As the American National Standards for the Safe Use of Lasers (ANSI) stated, the maximum permissible exposure (MPE) of the NIR-II light is several times higher than that of NIR-I light (e.g., 1 W/cm\(^2\) of 1064 nm NIR-II light vs 0.33 W/cm\(^2\) of 808 nm NIR-I light at the condition of skin exposure for 10 to 3 \times 10^4 s).\(^8\) This higher MPE, in turn, allows higher excitation power of NIR-II light to be applied for cancer nanotheranostics, which thus enables more effective activation of the nanoplatforms in vivo. In addition, the recent commercialization of affordable NIR InGaAs camera that is highly sensitive in the range of 900-1700 nm provides a powerful detection instrument to promote nanotheranostics in the NIR-II region, especially for those based on the fluorescence imaging (FLI).\(^9,10\) Realizing the extraordinary advantages of accomplishing cancer nanotheranostics in the NIR-II region, burgeoning research efforts were devoted to this field. This review aims to analyze the available imaging and
SCHEME 1  Cancer nanotheranostics in the second near-infrared window integrates diagnostics and therapeutics simultaneously to realize more efficient cancer treatment in deep tissue

therapeutic approaches to realize nanotheranostics in the NIR-II region, and to summarize the current applications of cancer nanotheranostics in the NIR-II region (Scheme 1). In the end, we will discuss the challenges and outlook the possible perspectives in the field.

2 IMAGING MODALITIES IN THE NIR-II REGION

The most widely applied imaging modalities in the NIR-II region include FLI and photoacoustic imaging (PAI). This is based on the light conversion ability of the contrast agent in the imaging module of the nanotheranostic platform. The contrast agent is usually composed of nanomaterials that can convert the incident light into either longer wavelength light emission or heat, which thus generate specific signals for imaging purpose.

2.1 NIR-II FLI

FLI uses the fluorescence emission from the contrast agents for imaging purpose. Due to its high spatiotemporal precision, noninvasiveness, and nonionizing features, FLI has been widely applied in both researches and clinics. The contrast agents for FLI are usually composed of fluorescent nanomaterials or dyes that effectively convert the incident excitation light into emission light at a different wavelength. This wavelength difference between the excitation and emission light is correspondent to the specific energy structures of the nanomaterial/dyes. Because the energy conversion usually involves nonradiative electron transitions in the materials, the wavelength of the emission light is usually longer than that of the excitation light. Thus, imaging by emissions located within the NIR-II region was generally recognized as the NIR-II FLI and within the scope of this review, regardless of the wavelength of the excitation light either in the NIR-I or NIR-II range. FLI is a widely used imaging modality in the NIR-II region that benefited from the fast development of the NIR-II fluorescent nanomaterials and dyes. Up to now, there were several types of materials that have been demonstrated for NIR-II FLI, such as semiconducting single-walled carbon nanotubes, quantum dots (QDs), lanthanide-doped nanoparticles, and organic dyes. Due to the minimized tissue scattering and absorption, these NIR-II FLI contrast agents provide significantly enhanced signal-to-noise ratio and has achieved high-quality imaging for a fine structure of vascular and tumor imaging in deep tissues.

2.2 NIR-II PAI

Different from the abovementioned fluorescent nanomaterials that emit NIR-II light upon excitation, some nanomaterials could convert the incident excitation light into heat, which could serve as the contrast agent for PAI. PAI emerges recently as a hybrid imaging technique taking advantage of both the high contrast in optical imaging and the high spatial resolution in ultrasound imaging. The PAI signals generate from the photoacoustic effect of intrinsic biological substrates or extra PA contrast agents, in which acoustic waves were produced by the thermoelastic expansion of stuff after absorbing short laser pulses. By using acoustic waves, which are less scattered by tissue compared to light, as the outgoing signal, PAI enjoys better lateral resolution and deeper imaging capability. Considering that biological tissue is usually transparent in the NIR-II region and cannot provide intrinsic contrast for imaging, PAI in the NIR-II region requires contrast agents to possess efficient photothermal effect upon irradiation of NIR-II light. Up to now, the library of NIR-II PAI contrast agents includes metal sulfides, noble metals, semiconducting polymer, and Mxenes. Photothermal effects of these materials could also be directly applied for the photothermal therapy (PTT) of cancers, thus making them intrinsically advantageous for cancer nanotheranostics by taking PAI as the imaging approach.

Although both FLI and PAI have been applied for the bioimaging in the NIR-II region, they have unique advantages for different application scenarios. For example, PAI takes light only for excitation and generates ultrasound for signaling, which attenuates little in tissue. Thus, PAI
is much more advantageous for deep tissue imaging compared to FLI, because FLI suffering light attenuation in both the in and out pathways. However, FLI is generally more capable for multiplex bioimaging than PAI. In FLI, multiple imaging contrast agents could be simultaneously excited by the same excitation light, and they have been differentiated by either the different emission wavelength or life time. Thus, the multiplexing FLI could be realized easily. In contrast, in PAI, the imaging contrast agents have to be differentiated by the different excitation light, which requires integrating multiple excitation light sources. It not only limits the multiplexing capacity of PAI but also makes the imaging system more complex. Thus, the selection of a proper imaging technique is essential to improve the diagnostic quality in the NIR-II region.

3 | THERAPEUTIC MODALITIES IN THE NIR-II REGION

As discussed above, the therapeutic effect of the nanotheranostic platform relies on the activation by the incident light. When light is absorbed by the platform, the energy could be converted into three forms: the longer wavelength emission, the heat, and energy for biochemical reactions (eg, generating active oxygen species). When considering the specific case of NIR-II light, because the biological tissue interacts extremely weakly with the emission, the emission can hardly serve for direct therapeutics. In addition, the energy of the NIR-II photon, from both the excitation and the emission light, is too low to initiate biochemical reactions. As a result, it is difficult to achieve photodynamic therapy in the NIR-II region. Fortunately, the heat induced by the incident light provides effective cancer therapies, either by PTT or by controllable therapeutic payload release.

3.1 | NIR-II PTT

PTT is a therapeutic modality that ablates cancers by the heat generated from photothermal nanomaterials upon light irradiations.\textsuperscript{45,46} The photothermal effect in tumors is significantly determined by the photothermal nanomaterials, the incident light wavelength, and the light delivery approach. An efficient PTT aims to uniformly increase the temperature in tumor tissues while avoiding damages to the surrounding healthy tissues. Due to the temperature gradient in tumor tissues, PTT usually needs to keep the tumor center above 50°C, to ensure that the tumor edges also fall in the therapeutic temperature range.\textsuperscript{45} Therefore, it is crucial to enhance the photothermal conversion of the PTT nanomaterials. Moreover, the absorption spectra of the nanomaterials are also important in PTT applications, especially for deep tissue tumor ablations. Many nanomaterials demonstrated strong photothermal conversion in the NIR-I range and have been applied for PTT applications in the last couple of decades, whose energy gaps are still relatively large to absorb NIR-II light. Thanks to the recent advances of the controllable engineering of the optical properties of nanomaterials, several strategies have been applied to narrow down their energy gaps, thus providing a growing library of PTT therapeutic agents in the NIR-II region. Similar to those photothermal nanomaterials used for NIR-II PAI, metal sulfides,\textsuperscript{37,38} noble metals,\textsuperscript{39} and semiconducting polymer\textsuperscript{40-43} are also widely applied for NIR-II therapeutics.

3.2 | Controllable therapeutic payload release

Beyond the direct cancer ablation by the heat generated by the PTT therapeutic agents under NIR-II irradiation, the heat could also be applied to induce a controllable therapeutic payload release to activate the downstream cancer treatment. In this case, the photothermal materials serve as a smart carrier, in which chemical drugs or immune checkpoint inhibitors are loaded. Upon the NIR-II light irradiation, these payloads were released at the tumor site for chemotherapy or immunotherapy, respectively. Compared to the direct administration of these payload, the release of them from a smart stimulus-responsive carrier could intentionally function at the target site and in a controllable manner. In this way, it minimizes the side effect from any off-target drug in the healthy tissue and could stop any overdose in real time. In addition, compared to the direct PTT, it enables customized therapeutics to effectively address the unique circumstance of the tumor. However, because it involves additional steps for payload delivery and release, thermal sensitive materials that perform formation transitions or decompositions are usually applied for the surface modification on the therapeutic module of the nanotheranostic platform.\textsuperscript{47,48} And it is worth noting that this strategy also suffers the same adverse effect of PTT to possibly overheat the ambient healthy tissue surrounding the tumor.

4 | CANCER THERANOSTICS IN THE NIR-II REGION

Through developing a nanotheranostic platform integrating the abovementioned imaging and therapeutic modalities, several demonstrations of cancer nanotheranostics have been achieved in the last 5 years, which could be
classified into the following categories: FLI-combined PTT, FLI-combined chemotherapy, PAI-combined PTT, PAI-combined chemotherapy, multimodal imaging-combined PTT, and imaging-combined synergistic therapies.

4.1 | FLI-combined PTT

Graphene quantum dots (GQDs) are a type of emerging optical biomaterials made of graphene nanoparticles (<100 nm) with pronounced quantum confinement effect. They possess good chemical and optical stability, excellent biocompatibility, and are easily cleared and excreted by the kidney. Recent studies also discovered photothermal ability within GQDs, thus applicable for nanotheranostics. Wang et al synthesized a type of GQDs exhibiting strong absorption at 1070 nm through a solvothermal method and using phenol as the precursor of controllable decomposition of hydrogen peroxide at a condition of a high magnetic field. They found that the as-prepared GQDs possess both a high quantum yield of 16.67% and high photothermal conversion efficacy of 33.45%, and thus are excellent for NIR-II cancer nanotheranostics. They demonstrated NIR-II FLI-combined PTT for cancer treatment both in cell experiments and in living mice.

PbS/CdS QDs were also applied for FLI-combined PTT in the NIR-II region. In a recent work, Cui et al synthesized PbS/CdS core-shell QDs possessing both NIR-II emission (~1600 nm) and good photothermal conversion property (47.6%). They conjugated the QDs with arginine-glycine-aspartate peptide for tumor targeting. They found that these QDs could monitor the abnormal angiogenesis and reduction of tumor-associated vessels through the NIR-II FLI. In addition, the PTT not only destroy the tumor tissue but also activate the immune response, to suppress the recurrence of tumor.

In addition to inorganic nanomaterials, organic fluorophores are also applicable for NIR-II cancer nanotheranostics. However, most of the NIR-II organic fluorophores are hydrophobic, thus limiting their applications in the biological environment. To address this problem, Yan et al conjugated a small-molecule NIR-II fluorophore (Flav7) with an amphiphilic polypeptide to render them water soluble. They found that the polymeric fluorophore self-assemblies into uniform micelles with a size of 90 nm in aqueous solution. More attractively, in addition to preserving the NIR-II photoluminescence property, these micelles also possess a high photothermal conversion efficiency of 42.3%. They demonstrated an effective FLI-combined PTT in mice modal in vivo.

Aggregation-induced emission (AIE) is an abnormal phenomenon in which certain organic fluorophores display higher photoluminescence efficiency in the aggregated state, as opposed to the aggregation-caused quenching it generally occurs with most fluorophores. Due to this unique luminescence property, AIE fluorophores have attracted increasing interest in bioimaging. Recently, Liu et al reported that AIE fluorophores could also be engineered to possess photothermal property, and thus they are applicable to nanotheranostics. They performed the study in a NIR-II fluorophore, BPBBT, which possesses both twisted intramolecular charge transfer (TICT) and AIE property (Figure 2A). They found that after binding human serum albumin with BPBBT, the planarity of BPBBT was changed and its intramolecular rotation is restricted, which alters to the AIE and TICT state equilibrium of BPBBT and makes it photothermal efficient (Figure 2B). The AIE fluorophores were accumulated in the tumor site of cecum, whose NIR-II luminescence provided more accurate and sensitive signal for tumor detections (Figure 2C). In addition, the TICT state of the nanoparticle enabled efficient ablation of the tumor (Figure 2D) and enhanced the survival rate of mice (Figure 2E). In this way, they completed an ablation of mice bearing colon cancer by the NIR-II FLI-combined PTT.

In order to enhance the specificity of the cancer nanotheranostics, researchers have developed nanoplatforms only active under certain circumstances. For instance, Fan et al designed a site-specific hydrogen sulfide (H₂S)-activatable NIR-II FLI-combined PTT nanoparticle for colorectal cancer (CRC). The H₂S activation is achieved through thiol-halogen nucleophilic substitution with H₂S in a monochlorinated BODIPY (boron dipyrromethene). After self-assembled into nanoparticles, with the presence of H₂S, it not only shows an efficient photothermal conversion but also exhibits bright luminescence in the NIR-II region under a 785 nm laser excitation. They demonstrated a specifically activated NIR-II FLI-combined PTT in H₂S-rich CRC, with normal tissues intact.

4.2 | FLI-combined chemotherapy

Apart from PTT, NIR-II FLI has also been coupled with chemotherapy for cancer nanotheranostics. For instance, Dai et al developed a novel nanotheranostic platform constructed by carboxylated poly(styrene-co-chloromethyl styrene)-graft- poly(ethylene glycol) (PS-g-PEG-COOH), the NIR-II organic dye with 3,4-ethylenedioxy thiophene as the donor and fluorene as the shielding unit (FE), and the anticancer drug paclitaxel (PTX). FE and PTX were encapsulated into the amphiphilic polymer, thus rendering them water dispersible (Figure 3A). After surface modification with folic acid to enhance the tumor-targeting ability of the nanoplatform, they administrated them to murine 4T1 tumor-bearing mice and achieved a high tumor to
normal tissue signal ratio of about 20 at the time point of approximately 24 h after injection (Figures 3B and 3C). They repeatedly administrated the nanocomposite at the time point of day 0, day 7, and day 14, and achieved a complete ablation of the tumor (Figures 3D and 3E).

### 4.3 PAI-combined PTT

PAI-combined PTT is the most widely used cancer nanotheranostics in the NIR-II region, due to the fact that both of the imaging and therapy could be achieved based on the photothermal property of the nanoplat-form without additional function requirements. For instance, semiconducting polymers have been widely applied to construct nanotheranostic platform based on PAI-combined PTT. Pu et al found that by inserting an extra D-A pain in the semiconducting polymer originally absorbing NIR-I light, its bandgap could be narrowed down for NIR-II light absorption. In this way, they engineered the NIR-I semiconducting polymer, poly[diketopyrrolopyrrole-altthiophene] (SPI) consisting of a D-A structure, into a NIR-II semiconducting polymer, poly[diketopyrrolopyrrole-altthiadiazoquinoloxaline] (SP2) consisting of a D-A1-D-A2 structure. Thus, they shifted the absorption band of the semiconducting polymer to the NIR-II region. They demonstrated a PAI at 3-cm tissue depth with 1.4 times enhancement of signal-to-noise ratio under a 1064-nm laser compared to that under 750-nm excitation. Moreover, an effective NIR-II PAI-combined PTT for tumor ablation was achieved in mice modal in vivo. By using semiconducting polymers with other molecular structures, Bian et al, Fan et al, and Yang et al also demonstrated independent researches exploiting the NIR-II PAI-combined PTT.41-43

To further enhance the controllability of the cancer nanotheranostic platform, Pu and Xing designed a tumor microenvironment-activatable NIR-II PAI-combined PTT platform.55 The platform is constructed by a folic acid-modified mesoporous silica that simultaneously loaded the enzyme horseradish peroxidase and its substrate, 3,3',5,5'-tetramethylbenzidine (TMB) (Figure 4A). The TMB oxidation could be activated by tumor environment pH to possess strong photothermal property in the NIR-II
region, thus enabling a specific “turn on” process with the presence of tumor microenvironmental redox parameter, \(\text{H}_2\text{O}_2\). Compared to the “always on” NIR-II nanotheranostics, the tumor microenvironmental-activatable nanoplatforn avoids the inherent nonspecificity resulted from the pseudosignal readout and is free from off-target-treatment-related side effects. They applied the nanoplatforn to demonstrate nearly zero-background PAI-combined PTT for efficient tumor ablation (Figure 4B) in the NIR-II region and with no effect on the mice growth curve (Figure 4C).

Apart from those organic nanomaterials, inorganic nanomaterials could also be applied for NIR-II PAI-combined PTT. For instance, Duan et al assembled multiple Au nanoparticles in polydopamine to form an Au plasmonic blackbody (AuPB). These AuPB exhibited strong and broadband absorption from the UV to NIR-II region (400-1350 nm) as a result of the intensive intraparticle plasmonic coupling between each Au nanoparticles. In addition, the self-polymerization of dopamine over the AuPB constructed a stable and biocompatible surface modification on it. Compared to the monodispersed Au nanoparticles, which only absorb NIR-I light, the AuPB demonstrated a much enhanced PAI-combined PTT for tumor at deep tissue owning to the excitation at the NIR-II region.

MXenes are an emerging type of two-dimensional nanomaterials that possess excellent photothermal conversion ability in the NIR region. Their broad absorption spectra could extend long into the NIR-II region. In a recent work, Huang et al found that the photothermal conversion of titanium nitride quantum dots (Ti\(_2\)N QDs) is as high as 45.51% under the irradiation of 1064-nm NIR-II laser. They synthesized the Ti\(_2\)N QDs through facile etch and exfoliate the bulk Ti\(_2\)AlN, followed by a probe and bath sonication to realize them 5 nm-sized QDs (Figure 5A). After injection into the mice, Ti\(_2\)N QDs accumulated in the tumor in 4 h for efficient PAI (Figure 5B) and PTT. The tumor ablation of the NIR-II treatment is significantly optimal.
4.4 PAI-combined chemodynamic therapy

In addition to PTT, chemodynamic therapy has also been demonstrated to couple with PAI for NIR-II cancer nanotheranostics by a controllable release of therapeutic payloads. For instance, Liu et al designed a metal-organic nanoparticles (NMOPs) by an assembly of Cu(II) ion and tetrahydroxyanthraquinone (THQ) into [Cu(II)-THQ]_{n} complexes via coordination through the van der Waals force and π-π interactions (Figures 6A and 6B).\textsuperscript{48} Under NIR-II excitation at 1064 nm, the NMOPs possess efficient photothermal property (with a conversion efficiency of 51.34\%) derived from the photoinduced electron transfer mechanism (Figure 6C) for PAI. At the same time, with the presence of the tumor acidic environment, Cu(II) gradually releases from the NMOPs through cleavage of the coordination bonds. The free Cu(II) induced Fenton-like reactions in tumor and generated •OH antitumor reactive oxygen species from H_{2}O_{2}, which effectively prevent tumor growth. In this way, PAI-combined chemodynamic therapy was achieved in the NIR-II region.

4.5 Multimodal imaging-combined PTT

Different imaging modalities possess unique capabilities in terms of tissue contrast, distinct sensitivity, and varied spatial/temporal resolution for bioimaging. Multimodal imaging integrates two or more imaging modalities at a time, thus emphasizing strengths of individual modalities and overcoming their shortcomings.

As mentioned above, nanomaterials could convert the incident NIR-II to both fluorescence emission and heat, which thus enables FLI and PAI dual modal-combined therapies. For instance, Chen et al synthesized Ag_{2}S...
**FIGURE 5** (A) Schematic illustration of biodegradable Ti$_2$N QDs for PAI-combined PTT in the NIR-I/II region. (B) PAI images in the tumor after tail vein injection at preset time intervals. (C) Time-dependent tumor growth curves in different groups of mice. Reprinted with permission. Copyright 2020 Elsevier

**FIGURE 6** Metal-organic particles for NIR-II PAI-combined chemotherapy. (A) Schematic illustration of the behavior of Cu(II)-THQ nanoparticles upon the 1064 nm laser irradiation in vivo. (B) Synthesis of Cu(II)-THQ nanoparticles by a one-step method. (C) Mechanism of Cu(II)-THQ nanoparticles transforming photoenergy to heat. Reprinted with permission. Copyright 2018 American Chemical Society
nanodots by controlling their growth in hollow human serum albumin nanocages (Figure 7A). They found that the fluorescence efficiency and photothermal property of the nanodots follow a size-dependent manner under NIR-II light irradiation. By carefully selecting the size of the nanodots, they effectively preserve both fluorescent and photothermal property in the same nanodots (Figure 7B). By using the fluorescence signal for FLI and the photothermal ability for PAI and PTT, they demonstrated FLI and PAI dual modal-combined PTT for tumor ablation in mice model (Figure 7B).

Apart from the internal combination of the FLI and PAI generated by the single NIR-II irradiation, imaging modality generated by other excitations could also be combined with the NIR-II-generated FLI and PAI. For instance, magnetic resonance imaging (MRI) could be easily incorporated by introducing magnetic components into the nanotheranostic platform. In a study by Huang et al, copper manganese sulfide (Cu$_2$MnS$_2$) nanoplates have been applied for the MRI-PAI dual modal-combined PTT. Compared to the conventionally used copper sulfide-based photothermal nanomaterials, the manganese dopant endowed the nanoplates with magnetic property, responsible for the MRI. Combined with its intrinsic photothermal property, which realized PAI and PTT in the NIR-II region, this nanoplatform enabled MRI-PAI dual modal-combined PTT in the NIR-II region. Following a similar idea, Fan et al fabricated a gadolinium-chelated semiconducting polymer for MRI-FLI-PAI trimodal-combined PTT in the NIR-II region, in which the paramagnetic gadolinium is responsible for MRI, by which the semiconducting polymer converted incident light into NIR-II emission and heat for FLI, PAI, and PTT.

4.6 Imaging-combined synergistic therapies

Introducing extra dopant not only enables multimodal imaging but is also applicable to include additional therapeutic approaches for synergistic therapies. For instance, Li et al prepared W-doped TiO$_2$ (WTO) nanoparticles. In this nanoplatform, the high-Z element, tungsten, not only serves as the contrast agent for X-ray computed tomography (CT) but also serves as the radiosensitizers...
to concentrate X-ray radiation in the tumor for efficient radiotherapy. Combined with the NIR-II photothermal property of TiO$_2$, which enables both PAI and PTT, WTO nanoparticles enable CT-PAI dual-modal imaging-combined synergistic PTT-radiotherapy. In another example, Jiang et al demonstrated an MRI-combined synergistic NIR-II PTT-chemotherapy of tumors. They fabricated the nanoplatform based on mesoporous silica, in which the NIR-II photothermal nanomaterial Au-Cu$_9$S$_5$, MRI contrast agent gadolinium, and an antitumor drug Doxorubicin hydrochloride (DOX) were loaded and coated by phase change materials for the heat-induced release of DOX (Figure 8). After absorption of the incident NIR-II light, Au-Cu$_9$S$_5$ generates heat for both PTT and release of the DOX for chemotherapy. With the Gd-based MRI ability, the nanoplatform enables MRI-combined synergistic PTT-chemotherapy of tumors in the NIR-II region.

Starvation therapy is an emerging cancer treatment to suppress tumor growth by blocking the energy supply in tumor. This is usually achieved by intentionally increasing the glucose oxidase (GOx) in the tumor site to convert glucose into gluconic acid and H$_2$O$_2$, thus creating “starvation” in tumor. In a recent work, Huang et al combined starvation therapy with chemodynamic therapy under the imaging by PAI in the NIR-II region. The sequential starvation-chemodynamic therapy was programmed by constructing a GOx-functionalized SrCuSi$_4$O$_{10}$ nanosheets (SC NSs) (Figure 9A). In this nanotheranostic platform, the SC NSs possess efficient photothermal conversion (46.3%) in the NIR-II region, thus enabling efficient NIR-II PAI. Additionally, this heat generation promotes the catalytic activity of GOx for enhanced starvation therapy. More importantly, the gluconic acid generated in the starvation therapy accelerated the degradation of SC NSs to release Sr and Cu ions. These ions enable the Fenton-like reaction for H$_2$O$_2$ generation to realize the chemodynamic therapy. Through this delicate design, both efficient PAI (Figure 9B) and starvation-chemodynamic synergistic therapy (Figure 9C) were achieved in the NIR-II region.

4.7 Other imaging modal-combined PTT

The photothermal ability of nanoplatform could be applied for thermal imaging-combined PTT without the emerging PAI technology, albeit at sacrificed resolution and specificity. For instance, Xu et al prepared two-dimensional ultrathin polypyrrole nanosheets possessing broadband absorption into the NIR-II region with an extinction coefficient of 27.8 L/g/cm at 1064 nm. They use direct thermal imaging-combined PTT for tumor ablation in mice model. Some of the nanotheranostic platform may be applicable for other imaging approaches. For instance, Wang et al prepared gold nanostars and found them possessing good photothermal properties in the NIR-II region as well as SERS imaging ability. Thus, instead of using the conventional FLI and PAI for imaging, they demonstrated cancer nanotheranostics through SERS-imaging-combined PTT. For some other studies, the imaging ability of the NIR-II nanotheranostic platform is originated from other imaging contrast agents. For instance, Wu et al fabricated a Fe$_3$O$_4$@Cu$_2$−$_x$S hybrid nanoparticle for MRI-combined PTT in the NIR-II region, in which the magnetic Fe$_3$O$_4$
introduced MRI, whereas \( \text{Cu}_{2-x} \text{S} \) is responsible for NIR-II PTT. In another example, Jiang et al fabricated an Au-Cu$_{9}$S$_{5}$ hybrid nanoplatform for X-ray computed tomography (CT)-combined PTT in the NIR-II region, in which the high-Z element Au introduced CT, whereas \( \text{Cu}_{2-x} \text{S} \) is responsible for NIR-II PTT.

5 | PERSPECTIVES AND CONCLUSIONS

Although encouraging progress was achieved in the last 5 years to develop cancer nanotheranostics in the NIR-II region, there were several challenges in further advancement.

The first issue lies in the sub-optimized nanomaterials properties. As discussed above, the properties of the nanomaterials constructing the nanotheranostic platform significantly determine the efficiency of the cancer nanotheranostics. However, because most of the current NIR-II nanotheranostic materials were derived from the NIR-I absorption materials with some modifications, their light absorption ability in the NIR-II region is limited. Thus, it is critical to exploit novel nanomaterials with tunable and enhanced light absorption in the NIR-II region, which will not only expand the choice of light source across the broader region in the NIR-II region but also enhance the cancer nanotheranostics efficiency. In addition, as the NIR-II nanotheranostic platform is majorly constructed by inorganic nanomaterials, whose biocompatibility is usually imperfect, researches to enhance their biocompatibility are urgently awaiting. A surface modification that could promote their excretion is essential to minimize side effects related to nanomaterial toxicity. However, there are very few studies addressing the toxicity, especially the long-term toxicity of these nanotheranostic platforms. In the meantime, exploring novel energy conversion modes, apart from photon downconversion and photothermal conversion, could also pave a new avenue for cancer nanotheranostics in the NIR-II region. In this regard, applying photon upconversion in the NIR-II region could convert the low-energy NIR-II photon into high-energy photon in the visible range, which could possibly be applied for photodynamic therapy or photoactivations for therapeutic purpose. Another alternative solution might be to develop therapeutic in vivo biochemical reactions that could be driven by the low-energy NIR-II photon to convert the energy into oxidation stress for therapeutic purposes.

The second issue could be exploring cancer nanotheranostics with other imaging and therapeutic modalities in the NIR-II region. As discussed above, due to the limited imaging and therapeutic approaches in the NIR-II region, there is a very limited combination for nanotheranostics. Especially for the therapeutic approaches, there are plenty of unexplored potentials. For example, for the NIR-II nanotheranostics with heat-induced therapeutic payload release, up to now, only chemodrugs were used as the payload for chemotherapy. However, gene therapy and immunotherapy, which are also effective cancer
treatments, have not been applied for cancer nanotheranostics in the NIR-II region. By changing the payloads to therapeutic genes or immune checkpoint inhibitors, extra therapeutic approaches could be applied for NIR-II cancer nanotheranostics. In the meantime, as discussed above, PDT should also be considered for NIR-II cancer nanotheranostics if upconversion nanomaterials that converting low-energy NIR-II photon into high-energy visible light photon coupled with correspondent photosensitizers could be used to construct the nanotheranostic platform.\textsuperscript{70,71} Once multiple therapeutic approaches are available in the NIR-II region, nanotheranostics utilizing synergistic therapies\textsuperscript{72,73} and programmable therapies\textsuperscript{74,75} should be considered to enhance therapeutic efficiency. In addition, multimodal imaging could also contribute to more efficient nanotheranostics, especially when the FLI and PAI, which are structural imaging techniques, combined with functional imaging techniques,\textsuperscript{76} such as MRI and positron emission tomography.

Cancer nanotheranostics in the NIR-II region has demonstrated extraordinary advantages over that in the shorter wavelength range. We believe, on the basis of the encouraging and fast-growing achievement and with the multidisciplinary effort from researchers in the fields of nanomaterial, optics, and nanomedicine, NIR-II cancer nanotheranostics will contribute more to the healthcare of human from the bench side to the clinical.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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