Nowadays, photodynamic therapy (PDT) is under the research spotlight as an appealing modality for various malignant tumors. Compared with conventional PDT treatment activated by ultraviolet or visible light, near infrared (NIR) light-triggered PDT possessing deeper penetration to lesion area and lower photodamage to normal tissue holds great potential for in vivo deep-seated tumor. In this review, recent research progress related to the exploration of NIR light responsive PDT nanosystems is summarized. To address current obstacles of PDT treatment and facilitate the effective utilization, several innovative strategies are developed and introduced into PDT nanosystems, including the conjugation with targeted moieties, O₂ self-sufficient PDT, dual photosensitizers (PSs)-loaded PDT nanoplatfor, and PDT-involved synergistic therapy. Finally, the potential challenges as well as the prospective for further development are also discussed.

1. Introduction

Photodynamic therapy (PDT) is considered as a promising minimally invasive treatment for various premalignant and neoplastic diseases. It requires three simultaneously present factors: a photosensitizer (PS), light source and molecular oxygen. The principle of PDT is based on introduction of the PS locally or systemically, and then followed by the irradiation of light with proper wavelengths on the lesion area. In this field, nontoxic PS will transfer its excited triplet state energy to the surrounding molecular oxygen or substrates such as molecules and cell membrane, thereby producing cytotoxic singlet oxygen (¹O₂) and other reactive oxygen species (ROS).3 PDT effects on tumor cells arise from the interaction of ROS with various biological targets, which are apt to destruction due to different reasons, such as the oxidation, disruption of homeostasis and ion transportation.4 The attractive feature of PDT is that photodynamic reactions just happen in the immediate locale of light-absorbing PSs. The in situ stimuli of light makes PDT destroy target tissue selectively while avoiding unnecessary side effects to healthy tissues. Compared with other traditional therapies, the noninvasive nature of PDT provides several outstanding advantages, including lack of systemic toxicity of drugs or radioactive rays, no long-time adverse effects, fast healing with little scarring and improved life quality of patients.4

In PDT, the depth of treatment effect hinges on the wavelength of light that irradiates PSs. However, due to the fact that most PSs clinically approved for PDT are prone to be activated by short-wavelength ultraviolet (UV) or visible (vis) light which cannot travel far into biological tissues, PDT modality is restricted to be a treatment for superficial lesions.4 The critical shortcoming of current PSs stimulates the research into the development of novel PSs which can achieve deep tissue treatment. In this respect, light penetration depth is strongly influenced by the light scattering and absorption within biological tissues.5 Notably, near infrared (NIR) light in the range of around 700–1000 nm, known as “the first NIR window” or “biological transparency window”, displays minimum photodamage to cells and better tissue penetration (e.g., <10 cm) than UV or vis light (e.g., <1 cm).6 Considering that, more attention has recently focused on to shift the excitation wavelength to NIR light for deep PDT treatment.

In recent years, significant efforts have been invested for the development of NIR light mediated PSs, in an attempt to broaden clinical applicability of PDT. Especially, numerous NIR-responsive organic molecules and novel nanoparticle-based PSs have been explored for NIR light induced PDT via direct energy conversion process. When illuminated by NIR light, these PSs can instantly respond to irradiated light and generate cytotoxic products effectively, thereby inducing cancerous cell death. In this field, continuous NIR laser with low energy density are commonly used to implement NIR-activated PDT treatment,
which exhibits little light-associated damage to the tissue that it passes across. In addition, two-photon excited PDT offers an alternative way for achieving deep PDT treatment triggered by NIR light. A series of organic compounds or nanoparticles with two-photon absorption, such as carbon nanomaterials, quantum dots, polymer nanoparticles and gold nanomaterials, have been studied as NIR light induced PSs.[7] It should be mentioned that this particular process can only be initiated by short-pulsed femtosecond NIR laser with high instant energy. Although two-photon excited PDT plays a considerable role in NIR light triggered phototherapy, this is beyond the scope of this review.

Moreover, another innovative strategy based on multiphoton excitation by upconversion nanoparticles (UCNPs) as nanotransducers has been emerging in the field of NIR-activated PDT. These UCNPs are excited by NIR light and can emit fluorescence across UV, vis, or even NIR range in accordance with the absorption characteristics of PSs. By the combination of UCNPs and classic potent PSs, these PSs could be “turned on” indirectly by NIR light and produce ROS via the fluorescence resonance energy transfer (FRET) mode. With the rapid development of synthetic and theoretical approaches, the emission range of UCNPs can be easily tuned by the type and amount of ions doped, which is advantageous to select available PSs as photosensitizing agents in this protocol. Thus there is a burgeoning interest in the development of UCNPs-based PSs for deep-tissue PDT.

Beyond the barrier of light penetration in tissue, the extent of photo-induced damage is also affected by other critical determinants such as the concentration and localization of PSs, the level of ROS generation, and its total influence in the region of interest. Correspondingly, much attention has devoted to construct novel nanosystems to overcome these limitations and promote efficacy of NIR light activated PDT. This present article covers the latest progress on NIR-activated PDT in biomedical applications and organized into four sections. The development of NIR light excited PSs (organic dyes and photosensitive inorganic nanoparticles) which could directly harvest NIR photons and generate ROS, and NIR-triggered UCNPs-based PDT nanosystems are discussed. Furthermore, the article highlighted the prominent problems in current PDT field, as well as emerging strategies to promote PDT treatment outcomes, including introduction of targeting agents, O2 self-sufficient PDT in tumor site and combination with other therapeutic modality. The last but not least, the possible antitumor mechanism of NIR-mediated PDT is presented, followed by the potential challenges and further perspectives for this promising PDT treatment. Our purpose is to provide a brief overview of NIR-mediated PDT systems, and we hope this review will inspire broader interests into the design of NIR-triggered nanomaterials for precise and effective cancer PDT.

2. NIR-Responsive PSs Based on Direct NIR Absorption

NIR-responsive PSs can absorb less-energetic NIR photons directly and conduct photochemical reaction to produce singlet oxygen. Recent accelerated progress indicates that there are at least two novel types of PS species with high molar absorption coefficient in the long wavelength above 700 nm. On one side,
inorganic nanoparticles with strong NIR absorption as PSs have been discovered recently. These nanoparticles are capable of producing \(^1\text{O}_2\) under irradiation of NIR light owing to their unique inherent properties, thus making them potential PDT agents by themselves. Such examples can be found in some nanomaterials, such as gold nanostructure and black TiO\(_2\). In this section, the detailed characteristics and properties of these NIR-mediated PSs based on direct NIR absorption are briefly reviewed.

### 2.1. NIR-Absorbing Organic Dyes

As mentioned above, a range of organic molecules have been synthesized and used for one-photon excited PDT by NIR light. So far, these available organic dyes include, but are not limited to, boron dipyrromethene (BODIPY) derivatives, cyanine dyes and phthalocyanine (Pc) derivatives.\(^8\) Some relevant examples covered in this section are shown in Table 1. Most of synthetic PSs are hydrophobic in nature with poor solubility in water. To improve their in vivo performance for PDT, hydrophilic nanoparticle-based carriers play a pivotal role in this field.\(^9\)

#### 2.1.1. BODIPY Derivatives

BODIPY derivatives are under extensive investigation as NIR-activated PSs.\(^10\) BODIPY dyes are one class of representative PDT agents with many ideal characteristics, such as high photostability, high extinction coefficients and fine-tuned photophysical properties.\(^11\) However, available BODIPY dyes are not effective for NIR-activated PDT since their absorption peaks are mainly located in the visible region. Nonetheless, through structural modification of BODIPY core with appropriate functional groups, the synthetic BODIPY derivatives could possess redshifted absorption maxima in the therapeutic window above 700 nm. Recent synthetic schemes have been adopted to make them promising candidates for NIR-absorbing PSs.\(^12\) For example, Huang’s group have synthesized bis-styryl BODIPY dye which exhibited longer wavelength absorption at 760 nm.\(^13\) After encapsulating the BODIPY dye within DSPE-mPEG5000, the resulting BODIPY NPs showed a strong NIR absorption peak at 775 nm, due to the intramolecular interaction between the dyes inside NPs. In comparison with commercial dyes, BODIPY NPs possessed better photostability. When irradiated by laser at 730 nm, these BODIPY NPs could be applied as acid-activatable PSs, and led to an effective PDT against A549 cancer cells. In PDT, the generated \(^1\text{O}_2\) is considered to be a crucial factor to induce irreversible damage to the cells. Highly efficient \(^1\text{O}_2\) generation ability of PSs is required to improve the therapeutic effect. For some PS dyes, the singlet-oxygen quantum yield can be tuned via the introduction of a heavy atom into dyes molecules, known as heavy-atom effect.\(^14\) This effect occurs since the heavy atoms enhance the spin-orbit coupling, resulting in faster rates of intersystem crossing (ISC) during the photochemical reaction. Therefore, novel NIR heavy-atom-substituted BODIPY dyes have been synthesized via the attachment of heavy atoms.\(^12a\) Liu et al. prepared a BODIPY-Br\(_2\) with strong NIR absorbance at 721 nm, which exhibited efficient \(^1\text{O}_2\) production under 808 nm irradiation (\(\Phi = 0.36\)).\(^15\) To develop a biocompatible and highly effective NIR-absorbing PS, Han’s group designed carbazole-substituted BODIPY (Car-BDP) molecules for PDT.\(^16\) These Car-BDP molecules presented a broad NIR absorption band and a remarkably high singlet-oxygen quantum yield (\(\Phi = 67\%\)).

### Table 1. Representative examples of NIR-excited organic dyes for PDT via direct energy conversion process.

<table>
<thead>
<tr>
<th>Organic PSs</th>
<th>Composite nanostructures</th>
<th>(\lambda_{\text{max}}) [nm](^a)</th>
<th>NIR laser [nm]</th>
<th>ROS yield</th>
<th>Laser dose [mW cm(^{-2})]</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>BODIPY derivatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bis-styryl BODIPY</td>
<td>BODIPY NPs</td>
<td>760</td>
<td>730</td>
<td>–</td>
<td>200 mW cm(^{-2})</td>
<td>[13]</td>
</tr>
<tr>
<td>BODIPY-Br(_2)</td>
<td></td>
<td>721</td>
<td>808</td>
<td>0.36</td>
<td>–</td>
<td>[15]</td>
</tr>
<tr>
<td>Carbazole-substituted BODIPY</td>
<td>Car-BDP-TNM</td>
<td>755</td>
<td>710</td>
<td>0.58</td>
<td>–</td>
<td>[16]</td>
</tr>
<tr>
<td>Cyanine dyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR780</td>
<td>IR780@PFTBA@BSA@HSA</td>
<td>~780</td>
<td>808</td>
<td>–</td>
<td>1 W cm(^{-2})</td>
<td>[18a]</td>
</tr>
<tr>
<td>IR780</td>
<td>HSA-780 NPs</td>
<td>~780</td>
<td>808</td>
<td>–</td>
<td>1 W cm(^{-2})</td>
<td>[18b]</td>
</tr>
<tr>
<td>IR820</td>
<td>IR820-CSQ@Fe@HSA</td>
<td>690</td>
<td>808</td>
<td>–</td>
<td>8 W cm(^{-2})</td>
<td>[19]</td>
</tr>
<tr>
<td>ICG</td>
<td>CS-Au@AuNR@HSA@HSA</td>
<td>795</td>
<td>808</td>
<td>–</td>
<td>2 W cm(^{-2})</td>
<td>[20a]</td>
</tr>
<tr>
<td>Br(_2)-IR808</td>
<td>Cysteine-loaded nanogel</td>
<td>808</td>
<td>808</td>
<td>0.046</td>
<td>200 mW cm(^{-2})</td>
<td>[21]</td>
</tr>
<tr>
<td>Iodinated derivatives of IR783 (6a)</td>
<td></td>
<td>~780</td>
<td>808</td>
<td>–</td>
<td>1.5 W cm(^{-2})</td>
<td>[22]</td>
</tr>
<tr>
<td>Heptamethine cyanine dyes (7)</td>
<td></td>
<td>~780</td>
<td>808</td>
<td>–</td>
<td>1.5 W cm(^{-2})</td>
<td>[25]</td>
</tr>
<tr>
<td>Pc derivatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicon 2,3-naphtho-cyanine dihydroxide</td>
<td>SiNC-Loaded IOCs@Au NPs</td>
<td>778</td>
<td>808</td>
<td>0.35</td>
<td>0.55 W cm(^{-2})</td>
<td>[31a]</td>
</tr>
<tr>
<td>Silicon naphthalocyanine bis(trihexylsilyloxide)</td>
<td>SiNC-NPs</td>
<td>782</td>
<td>785</td>
<td>–</td>
<td>1.3 W cm(^{-2})</td>
<td>[31c]</td>
</tr>
<tr>
<td>Silicon naphthalocyanine</td>
<td>SiNC-PNP</td>
<td>785</td>
<td>785</td>
<td>–</td>
<td>1.3 W cm(^{-2})</td>
<td>[32]</td>
</tr>
</tbody>
</table>

\(^a\)Peak absorption of PSs or PSs-loaded nanoparticle; \(^b\)Light dose for in vitro or in vivo experiments.
2.1.2. Cyanine Dyes

Typical cyanine dyes are a class of compounds with two aromatic nitrogen-containing heterocycles connected by a polythine bridge. This family of dyes is of particular interest due to their high extinction coefficients and spectral properties in the NIR region.\(^\text{17}\) Many of these dyes are commercially available and used for fluorescent labeling or analysis. To date, various cyanine dyes have been ascertained with the ability to produce \(\text{O}_2\) under NIR excitation, such as, IR780,\(^\text{18}\) IR820,\(^\text{19}\) and indocyanine green (ICG).\(^\text{20}\) To significantly enhance the efficiency of ROS generation, heavily metal-bromine substituted cyanine Br\(_2\)-IR808 dye\(^\text{21}\) and iodinated derivatives of IR783\(^\text{22}\) were also developed as above. In this respect, most of these dyes not only generate ROS under NIR light excitation, their energy from the excited singlet state may also convert into heat via non-radiative transitions process or vibronic relaxation, thus making them as more promising tools for synchronous cancer imaging and phototherapy.\(^\text{23}\) For example, classic cyanine dye ICG is a water-soluble dye and exhibits strong absorption around 780 nm. As a Food and Drug Administration approved diagnostic agent for clinical use, ICG has also been widely explored as NIR light activated agents for cancer therapy. In 2014, Cai’s group fabricated smart nanosystem by encapsulating ICG into endogenous protein human serum albumin (HSA) NPs for in vivo cancer theranostics (Figure 1a,b).\(^\text{20}\) The resulting HSA–ICG NPs exhibited improved cell uptake ability and enhanced cancer cell targeting ability. Moreover, by virtue of multifunctional property of ICG, these NPs could achieve fluorescence/photoacoustic (PA) imaging-guided precision phototherapy. These results suggested that ICG could act as an ideal theranostic platform. In addition, some cyanine dyes in their native forms could serve as superior PS with targeting properties. Several chemical structures have been verified with high specific targeting towards interested tissues, and it is reported that the unique property can be inherent to small NIR dyes containing these structures.\(^\text{24}\) For instance, Luo et al. synthesized a class of heptamethine cyanine dyes based on the mitochondria-targeted heptamethine core.\(^\text{25}\) In this research, compounds 7 was studies as multifunctional agents simultaneously with cancer cell mitochondrial targeting, NIR imaging and synchronous PDT/photothermal therapy (PTT) effects.

2.1.3. Pc Derivatives

Pcs possess chemical structures related to porphyrins, and exhibit optimal photophysical and photochemical properties in the area of PDT. Although some metal Pcs derivatives display increasing \(\text{O}_2\) efficiency, such as zinc phthalocyanine (ZnPc)\(^\text{26}\) and tetra-substituted carboxyl aluminum phthalocyanine (AlGnPc)\(^\text{27}\). The strong absorption band of these Pcs mainly locates in the 670 nm range. Limited studies reported that Pcs could serve as NIR light mediated PS. Peng et al. synthesized hollow silica nanospheres (HSNs) with a mean size of 35 nm as carriers of hydrophobic Pcs. The as-prepared Pcs@HSNs was found to have a high NIR absorption with a peak centered at around 760 nm. Upon 730 nm illumination, the efficacy of Pcs@HSNs as active PSs was verified.\(^\text{28}\) Besides, naphthalocyanines (Ncs), an extended Pc derivatives, exhibit strong absorption peak at even longer wavelengths (740–780 nm) than Pcs, due to the additional benzene ring attached to each isoindole sub-unit on the Pcs skeleton.\(^\text{29}\) The light penetration depth in this NIR region is approximately twice that of clinically used porphyrin-mediated PDT.\(^\text{30}\) Thus these favorable characteristics make Ncs excellent PS candidates. Recent reports indicated that silicon naphthalocyanine (SiNc), capable of absorbing the light in 750–800 nm, can be efficiently activated by NIR light to produce ROS.\(^\text{31}\) Moreover, these Ncs with higher extinction coefficients are also used as contrast agents in fluorescence imaging, which makes them promising multifunctional agents for optical imaging and phototherapies in biological tissues. For example, Taratula et al. reported a SiNc-loaded polymeric nanoparticles (SiNc–PNP) for imaging-guided combinatorial phototherapy (Figure 1c,d).\(^\text{32}\) Under 785 nm NIR light illumination, the developed SiNc–PNP exhibited excellent photostability, efficient generation of NIR fluorescence, ROS, and hyperthermia. After intravenous injection of SiNc–PNP, the in vivo tumors tissue could be delineated with NIR fluorescence, and completely eradicated by the NIR light induced PDT/PTT treatment with no tumor recurrence detected during 25 d. Moreover, this encapsulation strategy may provide a simple way for a variety of NIR phototherapeutic and imaging agents with intrinsic hydrophobic nature.

2.2. NIR-Excited Inorganic PSs

Despite the advances made in small organic dyes, their low extinction coefficients and poor photostability might pose an impenetrable obstacle to clinical application. In the past decade, there are certain inorganic nanoparticles, including TiO\(_2\), ZnO, and fullerene, are widely used as PS candidates in the PDT domain.\(^\text{13}\) These inorganic nanomaterials as PDT agents present several obvious advantages, such as less photobleaching, superior photostability, as well as easy functionalization with additive properties. However, their optical absorption properties are mainly in the short wavelength. In order to improve the photo-controlled treatment depth, plentiful inorganic nanoparticles responded to light in the NIR region have been developed and studied by researchers. Initially, these NIR light absorbing nanoparticles have attracted much attention as photo-induced candidates with light-to-heat conversion property for phototherapy. It was believed that the mechanism behind the photodamage effects was mainly by reason of PTT effect. However, other possible concomitant mechanisms may exist in the same nanosystem. Indeed, recent years have witnessed lots of these inorganic nanostructures also reported as nanomaterial-mediated PDT agents due to their optical absorption properties. By direct excitation of inorganic nanostructures using NIR laser sources, it allows cytotoxic \(\text{O}_2\) come into being through the energy transfer to oxygen. Such nanomaterials include gold nanomaterials, carbon nanostructures, copper sulfide nanoparticles, transition metal oxides. These works allows us to identify the importance of PDT effect in these established photothermal nanomaterials. In addition, the potential benefits for employing
these nanoparticles for PDT are highlighted in the following sections.

2.2.1. Gold Nanomaterials

Gold nanomaterials are one of the most important subjects in the current phototherapeutic research. The localized surface plasmon resonance (LSPR) properties of gold nanostructure can be readily tuned by controlling their morphologies, shapes or structures, thus the development of Au nanomaterials with LSPR peak in the NIR region is an area of increasing interest. Massive studies show that Au nanomaterials are capable of effectively converting NIR light into heat and induce tumor destruction under NIR light excitation. Recently, Au nanomaterials working in the NIR region have received considerable attention as potential PSs. Upon NIR light irradiation, Au nanomaterials themselves can convert surrounding O$_2$ to toxic $^1$O$_2$, and exert PDT effects for cancer therapy. Many types of Au nanostructures including gold clusters, nanorods, nanocages, nanoshell, and nanoechinus have been disclosed as NIR-triggered PSs and expected to achieve more
effective PDT treatment. In 2014, pioneering work of Hwang’s group presented the first example of nanomaterials-mediated PDT effect by Au NRs (Figure 1e,f). High level of ROS generated by Au NRs alone under 940 nm light emitting diode light irradiation was evidenced, which caused significant amounts of cellular death. Meanwhile, upon irradiated by 915 nm laser light with a low power density of 130 mW cm$^{-2}$, the effective Au NRs-mediated PDT effects could result in complete tumor destruction in mice model. Remarkably, this finding gave insight into differentiating PDT effect caused by Au NRs from its PTT effect. It was explained that the phototherapeutic effects of Au NRs can be switched from PTT to PDT by changing the wavelengths of photo-excitation light. In comparison to its PTT effect (780 nm, 130 mW cm$^{-2}$), Au NRs-mediated PDT effect was proven to be far more effective on the tumor destruction. In addition, the capacity of Au NRs as multiple color fluorescent cellular makers was also described. Therefore, these functional Au nanomaterials may open a new avenue to future cancer phototherapy.

2.2.2. Carbon-Based Nanomaterials

Carbon-based nanomaterials have been explored in a growing number of bioapplications, including drug delivery, diagnostics and PTT treatment. In the very last few years, some of them such as carbon nanotube, graphene oxide (GO), and fullerenes (C$_{60}$) have showed high potential as activatable PSs for PDT. Murakami et al. discussed the respective PDT and PTT effect of semiconducting- and metallic-enriched single-walled carbon nanotubes (s-SWNTs). By contrast, s-SWNTs in this study were able to generate ROS under 808 nm laser irradiation and exhibited the potential for PDT effect. After stabilized with high-density lipoprotein (HDL), s-SWNTs showed photo killing activity against cancer cells through O$_2$ generation. In Hwang group’s later work, nano-sized graphene oxide which can induce the generation of ROS as well as hyperthermia upon ultra-low doses of NIR light excitation (980 nm, 250 mW cm$^{-2}$) was reported for the first time. The combined PDT and PTT pathway of these GO-based nanomaterials could cause effective destruction of B16F0 melanoma tumors in vivo. In addition, a new graphene oxide-fullerene C$_{60}$ hybrid (GO-C$_{60}$) which enabled simultaneous PDT and PTT triggered by 808 nm NIR light were also disclosed. In this system, the covalent attachment of GO to C$_{60}$ activated the ability of C$_{60}$ to generate O$_2$ in near infrared (NIR) region. In vitro cytotoxicity study indicated that the synergistic effects of GO-C$_{60}$ led to superior performance in the inhibition of HeLa cells compared to both individually.

2.2.3. Copper Sulfide Nanomaterials

The photothermal effects of copper sulfide nanomaterials under NIR irradiation are well-documented. In 2015, an interesting finding illuminated plasmatic copper sulfide nanocrystals (Cu$_2$S NCs) also possessed intrinsic NIR induced photodynamic activity. Other than photothermal conversion, Cu$_2$S NCs concomitantly incurred elevated ROS levels under 808 nm laser excitation, resulting in the effective PDT effect. It was demonstrated that Cu(I) species can produce ROS in aqueous and biological media via a modified Haber–Weiss cycle. The Cu(II) from Cu$_2$S NCs could be reduced to Cu(I) by the in vivo substances such as ascorbic acid or glutathione, thus triggering above reactions to induce ROS production. The in vivo investigations demonstrated that combinatorial PDT and PTT effect of Cu$_2$S NCs gave rise to in vivo efficient tumor inhibition. Illumined by this study, copper sulfide nanostructures have been utilized as smart light driven sterilants in reproductive medicine owing to their synergistic effects. In another research, Hou et al. reported a multifunctional drug delivery system based on hollow mesoporous CuS nanoparticles to accomplish synergistic combination of chemotherapy, PTT and PDT.

2.2.4. Transition Metal Oxides

Some transition metal oxides which possess strong LSPR in the NIR region of light, have also been found to be capable of sensitizing the formation of O$_2$ such as molybdenum oxide, tungsten oxide, and black titania. For instance, polyethylene glycol (PEG) modified W$_{18}$O$_{49}$ nanowires (NWs) have been previously developed as 980 nm laser-driven PTT agents for cancer therapy in vivo. Later, Kalluru et al. demonstrated that these nanowires with high LSPR band gap at 980 nm (1.26 eV) could serve as PSs to activate the formation of O$_2$. By irradiation with 980 nm light (200 mW cm$^{-2}$), PEGylated W$_{18}$O$_{49}$ NWs induced a significant amount of cellular death and complete destruction of solid tumors in vivo by a PTT effect, in combination with a very small PDT effect. Due to high atom number of W element, these W-based nanomaterials could be promising agents for computed tomography (CT) imaging and radiation dose enhancement. Thus ultrathin polyvinylpyrrolidone (PVP)-decorated W$_{18}$O$_{49}$ NWs can serve as multifunctional nanoagents for CT imaging and photothermal/photodynamic/radiation synergistic cancer therapy. In addition, a single NIR laser-induced multifunctional nanoplatfrom based on black titania (B-TiO$_2$) was reported by Shi’s group. This PEG$_{5000}$-NH$_2$ modified B-TiO$_2$ exhibited excellent dispersity and a broad optical absorption property ranging from NIR to UV owing to the LSPR. After illuminated by 808 nm laser, B-TiO$_2$-PEG nanostructures were competent to simultaneously producing toxic ROS and hyperthermia for PDT and PTT. Both in vitro and in vivo investigations indicated that such single multifunctional B-TiO$_2$-PEG nanoplatfrom could achieve infrared thermal/PA imaging-guided simultaneous PTT/PDT.

2.2.5. Other Nanomaterials

Other emerging inorganic nanoparticles exploited for NIR light activated PDT, such as lanthanide-doped mesoporous silica frameworks (EuGdO$_x$@MSF), NaYbF$_4$ NPs, Cs$_x$WO$_3$ nanorods, and Cu$_2$(OH)PO$_4$ quantum dots (QDs), have been brought to the light. Table 2 shows recent examples of inorganic nanoparticles applicable for NIR light activated PDT. These fine works enable to expand the pool of NIR light activated inorganic photosensitizing agents to enhance the
capability of PDT in vitro or in vivo experiments. \[\text{5}\] Radiotherapy; \[\text{6}\] Magnetic resonance imaging.

### 3. UCNPs-Based PSs for PDT via FRET Mode

In recent years, significant efforts have been invested for the development of NIR light mediated PDT with UV-vis-responsive PSs via indirect energy conversion process, in an attempt to broaden clinical applicability of conventional PDT. A circuitous way is referred to utilize NIR-absorbing nanoparticles as energy transducer to indirectly perform a typical PDT treatment. The rapid development of UCNPs has provided unprecedented opportunities for traditional UV- or visible responsive PSs to realize NIR triggered PDT via FRET mode.\[\text{56}\] On account of fascinating energy transduction mechanism of UCNPs that could convert NIR light to multicolor upconversion emission, various conventional PSs can be applied to fabricate NIR-triggered PDT nanoagents indirectly.\[\text{57}\] For instance, Yb\(^{3+}/\text{Er}^{3+}\) doped UCNPs which remained frequently used in PDT application, could offer emitted light in the green (540 nm) and red region (660 nm). Among light in these spectrum, red upconversion emission is preferred by the majority of PS molecules due to their chemically inertness and porosity which is not subjected to swell or change with pH.\[\text{59}\] Numerous PSs could be accommodated in the interior of silica structure, either in silica matrix or within the porous. In 2007, Schofield’s group first reported a versatile PS based on NaYF\(_4\):Yb,Er UCNP for PDT at NIR light excitation.\[\text{60}\] In this study, UCNPs were coated with silica layer and then organic PS merocyanine 540 (MC-540) were doped into silica and porosity which is not subjected to swell or change with pH.\[\text{59}\] Numerous PSs could be accommodated in the interior of silica structure, either in silica matrix or within the porous. In 2007, Schofield’s group first reported a versatile PS based on NaYF\(_4\):Yb,Er UCNP for PDT at NIR light excitation.\[\text{60}\] In this study, UCNPs were coated with silica layer and then organic PS merocyanine 540 (MC-540) were doped into silica layer during the coating process. Due to the good overlap between the Er\(^{3+}\) characteristic emission of UCNPs around 537 nm and the absorption of MC-540, the \(\text{1O}_2\) generation from the

#### Table 2. Representative examples of NIR light excited inorganic NPs for PDT.

<table>
<thead>
<tr>
<th>Inorganic PSs</th>
<th>Nanosystem</th>
<th>NIR Light [nm]</th>
<th>Light dose[\text{d}]</th>
<th>PDT and Other Functions</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold nanomaterials</td>
<td>Au nanorods Lipid bilayer-coated Au NRs</td>
<td>915</td>
<td>130 mW cm(^{-2})</td>
<td>1) PDT+PTT; 2) Fluorescence imaging</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>Au nanocages AuNCs-PEG</td>
<td>808</td>
<td>23 mW cm(^{-2})</td>
<td>PDT</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Au nanoshell Lipid-coated Au nanoshell</td>
<td>980</td>
<td>150 mW cm(^{-2})</td>
<td>1) PDT+PTT; 2) Fluorescence imaging</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Au nanoechinus Lipid-coated Au NEs</td>
<td>915</td>
<td>130 mW cm(^{-2})</td>
<td>PDT+PTT</td>
<td>[39]</td>
</tr>
<tr>
<td>Carbon-based nanomaterials</td>
<td>s-SWNTs HDL-stabilized s-SWNTs</td>
<td>808</td>
<td>–</td>
<td>PDT</td>
<td>[40]</td>
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<tr>
<td></td>
<td>Graphene oxide GO-PEG-folate</td>
<td>980</td>
<td>250 mW cm(^{-2})</td>
<td>1) PDT+PTT; 2) Fluorescence imaging</td>
<td>[41]</td>
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<tr>
<td></td>
<td>CO-C(_6)</td>
<td>808</td>
<td>4 W cm(^{-2})</td>
<td>PDT+PTT</td>
<td>[44]</td>
</tr>
<tr>
<td>Copper sulfide nanomaterials</td>
<td>Cu(<em>{2-x})S NCs PEG-coated Cu(</em>{2-x})S NCs</td>
<td>808</td>
<td>0.6 W cm(^{-2})</td>
<td>PDT+PTT</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Hollow mesoporous CuS NPs</td>
<td>808</td>
<td>2 W cm(^{-2})</td>
<td>1) PDT+PTT+chemotherapy; 2) PA imaging</td>
<td>[46]</td>
</tr>
<tr>
<td>Transition metal oxides</td>
<td>MoO(<em>{3-x}) quantum dots MoO(</em>{3-x}) quantum dots</td>
<td>880</td>
<td>2 W cm(^{-2})</td>
<td>1) PDT+PTT; 2) PA imaging</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>B-TiO(<em>{2-x}) quantum dots B-TiO(</em>{2-x})-PEG</td>
<td>808</td>
<td>1 W cm(^{-2})</td>
<td>1) PDT+PTT; 2) Infrared thermal+PA dual-modal imaging</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>W(<em>{18})O(</em>{49}) NWs PEGylated W(<em>{18})O(</em>{49}) NWs</td>
<td>980</td>
<td>200 mW cm(^{-2})</td>
<td>PDT+PTT</td>
<td>[48a]</td>
</tr>
<tr>
<td></td>
<td>W(<em>{18})O(</em>{49}) NWs W(<em>{18})O(</em>{49})-PVP NWs</td>
<td>980</td>
<td>1.2 W cm(^{-2})</td>
<td>1) PDT+PTT+RT[\text{b}]; 2) CT imaging</td>
<td>[51]</td>
</tr>
<tr>
<td>Other nanomaterials</td>
<td>EuGdO(<em>{2})-MSF EuGdO(</em>{2})-MSF-DOX</td>
<td>980</td>
<td>130 mW cm(^{-2})</td>
<td>1) PDT+chemotherapy; 2) Fluorescence and MR imaging[\text{d}]</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>NaYb(<em>{4}) F(</em>{4}) NPs TWEEN-modified NaYb(<em>{4}) F(</em>{4}) NPs</td>
<td>980</td>
<td>366 mW cm(^{-2})</td>
<td>PDT</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td>Cs(<em>{3})WO(</em>{4}) Nanorods Cs(<em>{3})WO(</em>{4}) NR@PEM</td>
<td>880</td>
<td>2 W cm(^{-2})</td>
<td>1) PDT+PTT; 2) CT+PA imaging</td>
<td>[54]</td>
</tr>
</tbody>
</table>

\[\text{d}\] Laser light dose for in vitro or in vivo experiments; \[\text{b}\] Radiotherapy; \[\text{c}\] Magnetic resonance imaging.

Massive previous investigations illuminate organic PSs could be integrated with UCNPs for deep tissue PDT. For the construction of UCNPs-PS nanocomposite, three different PS loading strategies were mainly employed, namely physical encapsulation by silica shells, physical attachment by polymer layers, and covalent conjugation onto UCNPs by surface functionalization or chemical binding process.\[\text{26,58}\] Physical encapsulation by silica shell has drawn great interest for PDT application due to their chemically inertness and porosity which is not subjected to swell or change with pH.\[\text{59}\] Numerous PSs could be accommodated in the interior of silica structure, either in silica matrix or within the porous. In 2007, Schofield’s group first reported a versatile PS based on NaYF\(_4\):Yb,Er UCNP for PDT at NIR light excitation.\[\text{60}\] In this study, UCNPs were coated with silica layer and then organic PS merocyanine 540 (MC-540) were doped into silica layer during the coating process. Due to the good overlap between the Er\(^{3+}\) characteristic emission of UCNPs around 537 nm and the absorption of MC-540, the \(\text{1O}_2\) generation from the
nanocomposites excited by an infrared laser of 974 nm was verified. Encouraged by this, diverse PSs have been embedded into a dense silica shell for UCNP-based PDT, such as MB,[61] RB,[62] and silicon phthalocyanine dihydroxide.[63] However, the dense silica coating may have an impact on the efficiency of PDT due to the difficulty of ROS release. To optimize the PDT process, dedicate core--shell nanostructure with UCNP's core and mesoporous silica shell were widely exploited to encapsulate PSs.[64] By virtue of the channels and porous structures, mesoporous silica layer provides a general and facile way for entrapping PS molecules. These PSs include ZnPc,[65] Vitamin B12,[66] RB,[67] and MB.[68] To increase the loading capacity of PSs and improve PDT efficacy, Chen's group recently designed a novel rattle structure with a UCNP core and a benzene-bridged organosilica shell.[69] The interior cavity gave rise to a high loading amount of PSs (7.7 wt%) and could prevent self-aggregation of PSs. Moreover, in comparison to conventional core--shell structures, this novel strategy achieved higher FRET efficiency from UCNP s to PSs, which facilitated a large production of ROS and led to an enhanced PDT efficacy. In this case, could high dose effect of ROS really result in high PDT efficiency? Very recently, Chen et al. investigated the influence of PS payload or amount of ROS generation on the PDT via cellular experiments in vitro (Figure 2a).[70] In this study, three UCNP-based PDT with controllable payload of protoporphyrin IX were developed to adjust the efficiency of ROS generation. The in vitro results clarified that the efficiency of ROS generation did not significantly affect the capability of killing cancer cells.

Polymer layer coating on the surface of UCNP s is also an alternative way for PSs loading. These PS molecules were incorporated or wrapped into the polymeric structure via hydrophobic-hydrophobic interactions or electrostatic interactions. In general, UCNP s normally possesses a hydrophobic surface due to the hydrophobic alkane chains such as oleic acid. To transfer these NPs into aqueous phase, multiple polymers were coupled to UCNP s to form a hydrophilic layer on their surface. Therefore, hydrophobic PSs could be tightly attached on to the apparent hydrophobic oleic acid layer near the surface of UCNP s. A series of different polymers have been recruited to embed effective PSs, such as PEI,[71] Tween 20,[72] PEG derivatives,[73] chitosan coating,[74] silane,[75] PEG/PEI coating,[76] and gelatin.[77] In particular, Tian et al. proposed a new and efficient NIR photosensitizing nanoplateform based on α-cyclodextrin modified Mn-dopant NaYF4:Yb/Er UCNP s (α-CD-UCNP s) with strong red upconversion luminescence (Figure 2b–d).[78] In this report, hydrophilic α-CD could be coated onto oleic acid-UCNP s through a simple host-guest self-assembly method to form water-soluble α-CD-UCNP s. Consequently, three commonly used hydrophobic PSs, which efficiently absorbed red UCL emission peaked at 650–670 nm, could be easily entrapped into the oleic acid layer on the surface of UCNP s, including Ce6, ZnPc, and MB. Upon 980 nm laser irradiation, the effective generation of cytotoxic ROS by three different types of Ps@UCNP s complexes was confirmed due to energy transfer process between UCNP s and attached PSs. Moreover, this facile strategy enabled α-CD-UCNP s to achieve combined PDT and chemotherapy by co-loading DOX and Ce6 on their surface via hydrophobic interaction. In other ways, PS loading could also be realized by electrostatic interaction between the components with opposite charged.[79] Wang et al. reported UCNP s coupled with β-carboxyphthalocyanine zinc (ZnPc-COOH) for NIR-triggered PDT through direct electrostatic interactions.[80] The positively charged Ln3+ ions exposed on the surface of ligand-free UCNP s, could be able to directly attract electronegative PS molecules. Such close distance between UCNP s and ZnPc-COOH resulted in the highest energy transfer efficiency (96.3%) ever reported.

The approach of physical loading provides a simple method to keep PS molecules close to UCNP s, favoring the energy transfer between the two components. However, due to the relatively weak force to hold PS molecules in this nanosystem, the possible PS leakage would compromise PDT efficacy. To address this problem, covalent grafting was proposed to be an advanced strategy for incorporating PSs into UCNP-based nanomaterials.[81] This conjugation strategy generally depend on a carboximide crosslinking reaction between functionalized UCNP s and carboxyl group of PDT drugs, such as RB[82] and ZnPc(COOH)2.[83] In recent studies, Lu et al. fabricated a non-leaking PDT platform through a highly PEGylated mSiO2 shell on UCNP s and covalently bonded with RB by typical EDC/NHS coupling reaction.[84] This nanosystem showed negligible drugs leaking and the loading capacity of RB was determined to be 0.87 wt%. In a similar study, Yang et al. prepared silica-coated UCNP s with hypocrellin A covalently incorporated inside the silica shells for NIR light triggered PDT.[85] In these systems, a noticeable benefit of the UCNP s could be an excellent bioprobe for tracking the location of nanomaterials during the PDT process. However, due to significant absorption by PSs, the UC emissions for imaging signals are greatly weakened. Recently, Li et al. developed a PDT nanoplateform by covalently conjugating RB molecules with core–shell structure NaGdF4:Yb,Er@NaGdF4:Nd,Yb UCNP s (Er@Nd NPs) (Figure 2e).[86] In this study, RB-HA was first synthesized to improve the reactivity of carboxyl group, and then utilized to covalently link with PEI to obtain final Er@Nd-RB conjugates. Under 808 nm excitation, these Er@Nd-RB conjugates were able to generate simultaneous UC green emission for triggering PSs and downshifted NIR emission for monitoring PDT therapy process. Thus, this research offers an effective UCNP s-based system for achieving imaging-guided deep PDT.

### 3.2. Integration of Inorganic PSs with UCNP s

To date, some novel inorganic PSs which absorb UV light or visible light have also been incorporated with UCNP s for NIR light triggered deep PDT. These nanomaterials often serve as an amorphous or crystalline PS layer directly capped onto the surface of UCNP s to decrease the energy transfer distance. Inorganic PSs range from photocatalysts, fullerene derivatives and semiconductor nanomaterials. TiO2 is a prominent example of these. Since the nanocomposites coupling Yb3+/Tm3+ doped UCNP s with TiO2 have been demonstrated as feasible ROS generator under NIR light excitation, there has been a growing interest in developing these nanocomposite...
with elaborate structures and improved performance in PDT application.\cite{Zhang2014} In 2014, Zhang’s group reported a uniform core–shell TiO\textsubscript{2}-UCNPs nanocomposites with continuous layer of crystallized TiO\textsubscript{2}.\cite{Zhang2014} To avoid their large aggregates in the complex biological applications, these nanocomposites were further modified with PEG.\cite{Zhang2015} Under 980 nm light irradiation, the resulting PEGylated TiO\textsubscript{2}-UCNPs could generate significant amount of ROS, thereby inducing good therapeutic efficacy both in vitro and in vivo. However, the synthesis of core–shell nanostructures needs multiple steps, which will complex the PDT process. Recently, our group fabricated a novel UCNPs@TiO\textsubscript{2} nanoplatform based on crystallized shell of small TiO\textsubscript{2} NPs and upconversion luminescent enhanced Na\textsubscript{3}YF\textsubscript{4}:Yb\textsuperscript{3+},Tm\textsuperscript{3+}@NaGdF\textsubscript{4}:Yb\textsuperscript{3+} core for in vivo PDT (Figure 3a–d).\cite{Ouyang2017} These UCNPs@TiO\textsubscript{2} nanomaterials could lead to cancer cell death under NIR irradiation as a result of the relevant disruption of mitochondrial function and activation of caspases. In addition, compared with UV light irradiation, NIR light triggered PDT caused by UCNPs@TiO\textsubscript{2} showed greater tumor growth inhibition due to the deeper tissue penetration. Additionally, it is recognized that 980 nm laser light might cause obvious overheating effect when irradiated for a long time.

Figure 2. a) Schematic illustration of modified microemulsion approaches for coating silica and PS on upconversion nanoparticles. Reproduced with permission.\cite{Wang2017} Copyright 2017, Wiley-VCH. b) Schematic illustration of the α-CD surface functionalization procedure and the preparation of Ps@UCNP complexes. c) Schematic illustration of 980-nm NIR induced PDT using Ps@UCNPs. d) Loading capacities of three photosensitizers onto α-CD-UCNPs under different photosensitizer concentrations. Reproduced with permission.\cite{Wang2013} Copyright 2013, Wiley-VCH. e) Schematic diagram for the formation of the Er@Nd-RB conjugates. Reproduced with permission.\cite{Wang2016} Copyright 2016, American Chemical Society.
time or at high power density. In the view of this, our group also made an attempt to design an 808 nm NIR light mediated PDT using a well-defined core–shell structured UCNPs@mSiO₂@TiO₂ nanocomposite.[90] All these efforts expedite the progress of UCNPs-TiO₂ nanocomposites to be applied for NIR light induced PDT, thus conducting an optimal and effective PDT treatment in vivo.

Besides, other new types of inorganic PS (Y₂Ti₂O₇,[91] C₆₀MA,[92] g-C₃N₄,[93] etc.) have also been applied to fabricate NIR-mediated UCNPs-PS nanosystems, though rare. In this respect, our group proposed a NIR light mediated PDT nano-platform by integrating NaYF₄:Yb³⁺,Tm³⁺ cores. TEM images of NaYF₄:Yb³⁺,Tm³⁺@NaGdF₄:Yb³⁺ core–shell UCNPs. d) TEM images of NaYF₄:Yb³⁺,Tm³⁺@NaGdF₄:Yb³⁺@TiO₂ (UCNPs@TiO₂) core–shell NCs. Reproduced with permission.[89] Copyright 2015, American Chemical Society. e) Diagram of the synthesis of UCNPs-BPS. Reproduced with permission.[94] Copyright 2016, American Chemical Society.

Figure 3. a) Schematic illustration for the synthetic procedure of UCNPs@TiO₂ NCs. b) Transmission electron microscope (TEM) images of the original NaYF₄:Yb³⁺,Tm³⁺ cores. c) TEM images of NaYF₄:Yb³⁺,Tm³⁺@NaGdF₄:Yb³⁺ core–shell UCNPs. d) TEM images of NaYF₄:Yb³⁺,Tm³⁺@NaGdF₄:Yb³⁺@TiO₂ (UCNPs@TiO₂) core–shell NCs. Reproduced with permission.[89] Copyright 2015, American Chemical Society. e) Diagram of the synthesis of UCNPs-BPS. Reproduced with permission.[94] Copyright 2016, American Chemical Society.

With deeply understanding of tumor biology and mechanism behind PDT-based tumor destruction, some critical obstacles that hindered the effectiveness of current NIR-triggered PDT were gradually elucidated. For instance, the passive delivery via enhanced permeability and retention effect may be not applicable to all kinds of cancer and could not minimize collateral damage to adjacent normal tissues. The limitation of passive targeting gives rise to ineffective PDT results. Besides, most solid tumors are lack of sufficient oxygen supply, which also

4. Innovative Strategies to Construct NIR Light Triggered Enhanced PDT

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hampers the PDT treatment. Similar with the strongly oxygen-dependent ionizing radiation, anoxic regions will greatly limit the tissue damage derived from $^{1}O_{2}$ at most cases.\textsuperscript{[95]} To circumvent these intrinsic restrictions in the context of PDT, several novel strategies are motivated to further perfect NIR light triggered PDT treatment. In this section, these novel strategies including constructing PDT nanogenoates with precise targeting ability, increasing the level of oxygen within tumor, employing dual PSs-loaded nanoplatfrom and developing PDT-involving combined therapy, have been specially presented.

4.1. Targeted NIR-Triggered PDT

Considering the fact that ROS has short lifetime (<40 ns) and small active range (<20 nm) in PDT protocol, the photodamage is therefore both spatially and temporally restricted. Effective retention of phototherapeutic agent in the target site becomes a prerequisite to realize efficient clinical outcomes.\textsuperscript{[96]} To engineer and design schemes for site-specific targeted PS nanosystems, additional targeting moieties were usually grafted to the surface of nanotherapeutic agents for guiding their delivery to the lesion location or even specific organelles.\textsuperscript{[97]} Through these ways, it is expected to increase the concentrations of PS-loaded nanostructures in the desired area, thus causing enhanced PDT-induced cytotoxicity and reducing nonspecific toxicity, especially in case of systemic administration. In this case, we attempted to emphasize the efforts to construct tumor-targeted PDT nanosystem and specific organelle-targeted PDT nanosystem recently.

4.1.1. Tumor-Targeted PDT

For tumor-targeted deep-tissue PDT, a number of common chemical targeting molecules have been exploited to modify PDT nanosystem, such as folic acid (FA), peptides and antibodies. It depends on the target-specific recognition of some over-expressed cellular makers on cancerous cells via ligand-receptor interaction or antigen-antibody interaction. For instance, FA molecules have a high binding affinity to folate receptors (FR) that are up-regulated in diverse cancer cells (HeLa, B16-F0 melanoma cancer cells, etc.).\textsuperscript{[81b,98]} but not in most normal tissues. FA-conjugated nanostructures enable to selective accumulate into the target cells via endocytosis pathways. Zhang and colleagues demonstrated FA-functionalized NaYF$_4$:Yb$^3$+Er$^{3+}$-RB nanoconjugates for improving the targeting efficacy in JAR choriocarcinoma cells.\textsuperscript{[81a]} The in vitro results verified their capability of efficient endocytosis and PDT effect specific to cancer cells under 980 nm light irradiation. In another similar research, Cui et al. applied FA ligand modified chititin (FASOC) to develop a UCNPs-based nanosystem for in vivo targeted deep-tissue PDT (Figure 4a–c).\textsuperscript{[99]} FASOC was coating on the surface of OA-UCNPs and ZnPc subsequently was encapsulated into the FASOC layer through hydrophobic interaction. The resulting FASOC-UCNP-ZnPc exhibited enhanced intracellular uptakes by in vitro FR-positive tumor cells and high tumor targeting ability in tumor bearing mice. The FRET-based PDT after 980 nm light irradiation resulted in higher tumor inhibition ratio (50%) for deep tumor model covered with 1 cm tissue, over than that of 660 nm induced traditional treatment (18%).

Peptides and antibodies were other appealing targeting ligands for PDT nanoplatfrom. In the field of peptides, RGD (arginine-glycine-aspartic acid) peptide has been identified as a notably effective tumor-penetrating peptide. It has a high affinity toward the $\alpha v \beta 3$ integrins that are specifically expressed on tumor vascular endothelial cells and many types of tumor cells.\textsuperscript{[100]} There has been extensive interest in the study of tumor-specific increase in tumor tissue access mediated by RGD peptide.\textsuperscript{[101]} Regarding NIR-triggered PDT, our group designed RGD peptide-modified UCMPs-ZnPc nanoplatform for targeted PDT treatment.\textsuperscript{[102]} Another study of c(RGDyK) modified UCNPs (R-SUZn nanoconstruct) for NIR light activated PDT system was reported by Gao et al.\textsuperscript{[73a]} The in vitro results validated the enhanced targeting ability of R-SUZn in $\alpha v \beta 3$ overexpressed PC-3 tumor model. In other side, much attention has also been paid on antibodies to act as specific target moieties for improving efficacy of deep-tissue PDT.\textsuperscript{[60,62]} Owing to high affinity of antibody-antigen interactions, the PS-loaded nano-system functionalized with antibodies could gain an increasing chance to accumulate in tumor sites. Zhang’s group designed a protein Affibody was aimed to specifically target epidermal growth factor receptor.\textsuperscript{[86c]} Zeng et al. reported UCNPs@Ce6@mSiO$_2$ nanoplatfrom linked with site-specific peptide ligands for targeting HER2-overexpressed breast cancer.\textsuperscript{[103]}

Apart from conventional molecular tumor targeting above, emerging researches suggest that some certain cells with tumor-tropic properties are capable of selectivity delivering NIR light activated PDT nanogenoates to the tumor site recently. This new strategy owes to the development of biomimetic-camouflage delivery system by coated with cell membranes. In the meantime, their attractive properties also bring nanoagents with inherent biocompatibility and long systemic circulation. These cells include mesenchymal stem cells (MSCs),\textsuperscript{[104]} leukocytes,\textsuperscript{[105]} and erythrocytes.\textsuperscript{[106]} Among these cells, MSCs have a natural high tumor affinity, providing a promising means for guiding nanomaterials directly to the tumor. The in vivo performance of using MSCs as a PS carrier for targeted breast cancer were confirmed.\textsuperscript{[107]} In recent study, Gao et al. demonstrated MCS membrane-cloaked PDT system to enhance therapeutic results (Figure 4d–f).\textsuperscript{[108]} The resulting nanoplatfrom SUCNPs@mSiO$_2$ was fabricated by fusing the stem-cell-membrane vesicles with dual-PS-loaded UCNPs@mSiO$_2$, which could serve as an intravenous injectable antitumor agent for NIR-activated PDT. In vitro and in vivo studies demonstrated that this novel nanoplatfrom exhibited remarkable accumulation at the tumor site, while the 980 nm light-excited PDT treatment induced enhanced anticancer efficacy by systemic administration. Although these finding have demonstrated the efficacy of MSCs for tumor targeting, its mechanism behind has still not been clarified.

4.1.2. Organelle-Targeted PDT

Currently, pioneering works revealed that design of organelle-target PSs nanosystem could further improve the efficacy of PDT.\textsuperscript{[109]} It is believed that the location of PSs in different
organelles makes great different in PDT outcomes. Several hypersensitive organelles within cancer cells, such as mitochondria\textsuperscript{[110]} and nuclei,\textsuperscript{[111]} were reported to be critical parts of ROS-induced damage. In particular, mitochondria were clarified as the ideal target site for PDT since these subcellular organelles play a crucial role in cell apoptosis. In contrary to PDT performed in cytoplasm, the generated ROS in the mitochondria can rapidly damage its function and induce the alteration of mitochondria membrane potential, thereby leading to apoptosis of tumor cells. Mitochondrion-targeted ligand triphenylphosphine (TPP) was extensively modified to these PDT nanoplateform.\textsuperscript{[6,112]} Yu et al. presented a NIR-responsive nano-photosensitizer based on mitochondria targeted TiO\textsubscript{2}-coated UCNPs for PDT\textsuperscript{[113]} The TPP group was modified on the surface of TiO\textsubscript{2}-coated UCNPs, which empowered PDT nano-system with capability to specifically localize in mitochondria of living cells. Upon irradiation of NIR light, intercellular UCNPs-based nanomaterials can selectively trigger the mitochondrial ROS burst and induce a series of cascade reaction, thereby inducing excellent in vitro and in vivo therapeutic efficacy (Figure 5). Besides, some functional ligands were also proved as feasible mitochondrial-targeted moieties for NIR-trigger PDT, such as trans-activating transcriptional activator (TAT) peptide\textsuperscript{[114]} and NIR dyes themselves as mentioned before.\textsuperscript{[25]}

Figure 4. a) Schematic of the synthesis of FASOC-UCNP-ZnPc nanoconstruct and folate-mediated binding of tumor cells with folate receptor expression. b) Particle size of the prepared nanoconstruct by DLS and TEM measurement. c) Semiquantification of FASOC-UCNP-ICG and SOC-UCNP-ICG in the isolated organs of mice with different injection. Reproduced with permission.\textsuperscript{[99]} Copyright 2013, American Chemical Society. d) Fabrication process of SUCNPs@mSiO\textsubscript{2} and its mechanism in PDT. e) TEM images of SUCNPs@mSiO\textsubscript{2}. f) In vivo images of mice at 1, 2, 4, 8, 12, and 24 h after tail vein injection of Cy7-SUCNPs@mSiO\textsubscript{2}. An equal amount of Cy7-UCNPs@mSiO\textsubscript{2} was injected into another group of mice as a control. Reproduced with permission.\textsuperscript{[108]} Copyright 2016, American Chemical Society.
4.2. O2 Self-Sufficient PDT

PDT is an oxygen-dependent process. Studies of tumor microenvironment demonstrated that the excess cancer cell proliferation and abnormal blood tumor vessel development would result in oxygen deficiency in the core part of most solid tumor. Moreover, the consumption of oxygen during PDT process further potentiates the extent of hypoxia. Therefore, to alleviate tissue anoxic levels has been an area of intensive study to enhance NIR-triggered PDT effects. Several outstanding works shed light on two possible approaches to achieve these goals: delivering O2 to tumor sites, or in situ O2 generation within hypoxia tumor. Beyond these conventional methods, a novel therapeutic strategy based on generation of oxygen-irrelevant free radicals was recently reported for evading tumor hypoxia situation.\[^{[115]}\] Upon 808 nm light irradiation, the generated free radicals (alkoxyl radicals or alkyl radicals) in this nanosystem exhibited equivalent therapeutic efficacy under both normoxic and hypoxia conditions with a different mechanism, which may open a new way to improve the therapeutic outcomes.

Figure 5. a) Schematic illustration of the structure of the nano-photosensitizer (TPP anchored UCNPs@TiO2 nanoparticles and ROS generation. b) Schematic diagram of the near-infrared triggered nano-photosensitizer inducing domino effect on mitochondrial ROS burst for cancer therapy. c) High resolution transmission electron microscopy images of OA-capped NaYF4:Yb3+,Tm3+. d) High resolution transmission electron microscopy images of OA free NaYF4:Yb3+,Tm3+. e) High resolution transmission electron microscopy images of UCNPs@TiO2. f) Schematic illustration of the structure of UCNPs@TiO2-TPP-IR806 and UCNPs@TiO2-TPP-HE, and structure formulas of IR806 and HE are showed on the bottom. g) Mitochondrial targeting of nano-photosensitizer under confocal imaging. MCF-7 cells were incubated with UCNPs@TiO2-TPP-IR806 for 12 h before measurement. Reproduced with permission[^113]. Copyright 2015, American Chemical Society.
4.2.2. In Situ O2 Generation in Hypoxic Tumor

Artificially delivering molecular O2 to the desired sites is one possible way to increase the PDT efficacy. However, it is a great challenge to design a nanoplatform which could carry a massive amount of O2 to the living tissue. In this regard, the first natural carrier for O2, red blood cells (RBCs), comes into chemical researchers’ mind. The intrinsic property of RBCs, carrying 270 million hemoglobin (Hb) molecules (each one can reversibly bind 4 O2) per cell, is the main source of oxygen to our body tissues. To date, some important advances in the combination of RBCs with PSs have been made for facilitating NIR-triggered PDT treatment. For this purpose, RBCs were employed to serve as O2 microcarriers, and organic PSs-loaded nanoagents were generally conjugated onto their surface via avidin-biotin-mediated coupling. Under low oxygen condition, efficient O2 generation by the resulting complex for enhanced PDT has been confirmed.[116] To realize selectively O2 delivery in hypoxia tumor, Zhang’s group developed an intelligent RBC-based microcarriers consisting of site-specific hypoxia probe HP and RB functionalized orthogonal excitation-emission UCNPs (Figure 6a–f).[117] The unique UCNPs possessed two independent emission under different NIR laser (980 or 808 nm) excitation, while the corresponding emissions could trigger HP or PDT treatment, respectively. Through activated by the hypoxia environment plus 980 nm laser light, HP could trigger O2 release from oxygenated hemoglobin in RBC microcarrier. Accordingly, the efficacy of 808 nm driven PDT could be greatly improved as a result of the increasing O2 in the tumor site. In another work, nanocarrier was also developed to act as artificial red cells for loading Hb. Cai et al. reported a biomimetic lipid–polymer nanoparticle by loading complexes of PS (ICG) and oxygen-carrier (Hb), to incorporate O2 supply and boost the efficacy of PDT.[118] In this research, the lipid layer was designed with oxygen carrying function similar to RBCs. After 808 nm laser exposure, ICG was able to produce massive ROS under the circumstances of sufficient O2 supply.

Besides, perfluorocarbon emulsions have been clinically investigated as an artificial oxygen carrier to improve tissue oxygenation.[119] These colorless liquids could physically dissolve significant quantities of oxygen. Unlike O2 transport behavior of blood, these emulsions possess a linear relationship between O2 partial pressure (PO2) and O2 content.[120] Higher PO2 value will result in superior O2 transport capacity of perfluorocarbon emulsions. Recently, efforts have been made to design these O2 reservoirs to instantly overcome the hypoxia-associated resistance of tumor.[121] Cheng et al. created a novel PS-loaded agent LIP(IR780+PFH) by encapsulating NIR-absorbing PS IR780 and perfluorocarbon into lipids to achieve oxygen self-enriching PDT (Oxy-PDT) (Figure 6g–l).[122] When irradiated by 808 nm laser, PS could transfer energy to O2 enriched in PFH to accelerate ROS generation. A higher therapeutic efficacy of Oxy-PDT over than tradition PDT was verified by the both in vitro and in vivo results, therefore showing this design could realize high efficacy in hypoxic condition.

4.2.2. In Situ O2 Generation in Hypoxic Tumor

Different from normal tissues, solid tumor generates excessive amount of endogenous substance such as H2O2. Researchers attempted to utilize these endogenous substances as a stimulus to activate O2 generation in situ. For instance, catalase was introduced into PS-loaded nanosystem to achieve self-sufficiency of O2 in hypoxic tumor cell.[123] When the intracellular H2O2 penetrates into the nanosystem, it could be catalyzed by this protein to generate O2 at the hypoxic tumor site. Therefore, PDT treatments will benefit from this reaction. Otherwise, MnO2 nanomaterials were evidenced to improve oxygenation in vivo on account of its unique reactivity with H2O2 to sustainably produce O2.[124] Gao et al. reported an oxygen-generating PDT nanocomplex based on MnO2 nanoparticles, which facilitated the enhanced PDT efficacy (Figure 7).[125] This hybrid nanocomplex was synthesized via encapsulating MnO2 nanoparticles in an ICG modified hyaluronic acid nanoparticles (HANP). In this complex, ICG served as a NIR-activated PS and IHM can be broken up by hyaluronidase in tumor. Thus MnO2 nanoparticles can be released after hyaluronidase degradation, and capable of react with H2O2 to generate O2 with high reactivity. In vivo studies revealed that the O2 content in the tumor could be elevated 2.25 times over that without IHM-based PDT treatment, implying this nanocomplex can effectively attenuate tumor hypoxia. After 808 nm laser irradiation, IHM-based PDT treatment induced significant tumor growth inhibition. Hence, all these fascinating findings may give new insight of improved PDT under oxygen deficient condition.

4.3. Dual PSs-Loaded PDT Nanosystems

For boosting UCNPs-based PDT outcome, one feasible approach is to enhance the match between the wavelength bands of UCNPs emission and PSs absorption. Given that the simultaneous multiple emission of UCNPs, PDT efficacy can be amplified through dual-PSs loading strategies. According to Zhang’s research, UCNPs-based nanosystem with two different PSs loaded was capable to realize better PDT therapeutic efficacy.[98b] Taking advantage of the multicolor-emission ability of NaYF4:Yb,Er in the presence of 980 nm laser light, these loaded MC540 and ZnPc molecules into mesoporous silica shell could be activated at the same time. The in vitro results validated that the co-loaded UCNPs resulted in reduced cell viability compared with single PS loaded UCNPs. Inspired by this, our group developed a series of nanomaterials for integrating two types of PSs to enhance the PDT therapeutic outcome.[126] For instance, two efficient PSs, TiO2 (UV-light excited inorganic PS) and hypocerin A (blue-light excited organic PS, HA) have been combined with UV-blue upconversion emitting UCNPs to form the UCNPs@TiO2@HA NCs (Figure 8a–d).[127] In this construction strategy, crystalized TiO2 shells could play dual roles as UV-light excited PS and conjugation site for Hyaluronic acid (Hyal), and then Hyal was served as targeting-ligand as well as HA carrier simultaneously. Due to the modification of targeting-ligand of Hyal and introduction of second PS of HA, UCNPs@TiO2@HA dual-PSs system can not only avoid administration of multiple doses of agents to minimize the side effects, but also dramatically improve therapeutic efficacy due to the enhanced generation of ROS. Furthermore, a critical issue for UCNPs-based PDT is how to develop UCNPs with high upconversion quantum efficiency.
Figure 6. a) Stepwise engineering of NIR-controlled orthogonal excitation-emission UCNPs anchored RBC microcarrier. b) Energy-transfer mechanisms of orthogonal excitation-emission upconversion luminescence: 480 nm UCL under 980 nm irradiation for oxygen release, 550 nm UCL under high power density of 808 nm irradiation for photodynamic therapy, 1060 nm DCL under low power density of 808 nm irradiation for downconversion bioimaging. c) SEM image of RBC microcarriers. Insert, magnification image of one RBC microcarrier attached with UCNPs (black arrows). d,e) CLSM images of obtained RBC microcarriers under 980 excitation in dark field and merge. f) In vitro evaluation of O$_2$ generation by incubating RBC microcarriers, RBC microcarriers without HP and pure RBC with hypoxia and normoxia U87MG cells. Reproduced with permission.[117] Copyright 2017, Elsevier. g) Structure and design of the Oxy-PDT agent. Photosensitizer and perfluorocarbon are coencapsulated by lipids. Photosensitizer is uniformly dispersed inside the lipid monolayer and PFC in the core of the nanoparticle. When irradiated by laser, PS transfers energy to the oxygen enriched in PFC, producing 1O$_2$, resulting in enhanced tumor inhibition. h) Dynamic light scattering of the Oxy-PDT agent. i) 1O$_2$ production of LIP(IR780+PFH) (16.7 µg mL$^{-1}$ IR780, 30% (v/v) PFH), LIP(IR780) (16.7 µg mL$^{-1}$ IR780), and water under different laser irradiation exposures. j,k) Cells were exposed to 2W cm$^{-2}$ of an 808 nm NIR laser for 20s, and viability was measured by the CCK-8 assay: CT-26 cells, and CT-26 cells in hypoxic conditions. l) Changes in tumor volumes used to assess the effectiveness of Oxy-PDT in tumor-bearing mice by intravenous injection. Treatments were performed only once. Reproduced with permission.[122] Copyright 2015, Nature Publishing Group.
With knowledge of NIR dye-sensitized core–shell UCNPs which could realize an upconversion quantum efficiency as high as 19%, our group introduced IR808-sensitized UCNPs (NaGdF₄:Yb,Er@NaGdF₄:Nd,Yb) for in vitro and in vivo dual-PS PDT (Figure 8e–g).[128] Carboxylic-functionalized IR-808 dye was first covered on the NOBF₄ ligand-modified UCNPs. After further encapsulated of a mesoporous silica shell on the UCNPs-IR-808, this resulting UCNPs@mSiO₂ nanosystem was capable to load Ce6 and MC540 via covalent conjugation and electrostatic interaction, respectively. This strategy realized an effective PDT effect under 808 nm laser excitation with relatively low power density (0.72 W cm⁻²). The dual PSs-loaded nanoparticles caused significant ROS generation, and higher PDT efficacy on tumor inhibition compared to single PS-loaded nanosystem was also validated by in vivo investigations.

4.4. PDT-Involved Synergistic Therapy

In spite of the encouraging therapeutic results in the previous studies, in vivo complete tumor eradication is not always fully achieved via individual PDT treatment. One booming area today is the studies on the combination of PDT with other therapeutic approaches. Through different treatment mechanisms, synergistic therapy is enable to make each treatment cooperative, which might offer potential advantages over a single therapy, since the tumor is unlikely to have resistance to multiple drugs simultaneously. Previous investigations testified that PDT-involved synergistic therapy could not only achieve enhanced therapeutic outcomes under low injected dose of therapeutic agents or low density power of laser excitation, but also maximally reduce the potential adverse effects to normal tissues. Up till now, versatile therapy modalities were explored to integrate with PDT for fighting against malignant tumor, such as chemotherapy,[129] PDT,[130] radiotherapy,[124a] or even immunotherapy[131] and gene therapy.[132]

4.4.1. PDT/Chemotherapy Dual-Modal Therapy

Many preclinical studies demonstrated that the combination of chemotherapy and PDT have exhibited a synergistic effect for both in vitro and in vivo cancer therapy.[133] The reason behind may be that chemo drug appears to improve tumor resistance to PDT in hypoxic tumor and prevent tumor regrowth, meanwhile the ROS generated by PDT in turn enhances the anti-tumor response of chemo drugs.[134] Therefore, co-delivery of PSs and chemo drugs into tumor might provide a promising way for better cancer therapy, such as potent anti-tumor drug doxorubicin (DOX).[135] Pt-prodrug[136] and AB3.[137] In this point, Zeng et al. fabricated a DOX loaded, folic acid targeted NaYF₄:Yb/Tm-TiO₂ (FA-NPs-DOX) nanocomposite for NIR light triggered PDT and chemotherapy.[86d] This investigation showed that combined therapy were capable of overcoming multidrug resistance of cancers both in vitro and in vivo (Figure 9a). Considering the tumor microenvironment and trait of PDT process,
Figure 8. a) Illustration of 808 nm laser-induced dual-agent photosensitizing nanoplatform by combining UV-blue UC emitting multi-shell UCNPs with TiO$_2$ (UV-light-excited PS) and HA (blue-light-excited PS). b) TEM of UCNPs@TiO$_2$ NPs. c) The upconversion emission spectra of UCNPs, UCNPs@TiO$_2$ and UCNPs@TiO$_2$@HA with the digital and luminescence photographs. d) The changes of tumor volumes on different groups after various treatments, $n = 6$. Reproduced with permission. Copyright 2016, Elsevier. e) Schematic illustration of IR-808-sensitized UCNPs with mesoporous silica and the dual-photosensitizer loaded imaging-guided PDT. f) Upconversion emission spectra of IR-808-sensitized UCNPs, UCNPs@mSiO$_2$, UCS, and UCSM and UV–vis absorption spectra of Ce6, MC540, and UCSM. g) Changes in the relative tumor volume achieved from mice with varying treatments. Reproduced with permission. Copyright 2017, American Chemical Society.
several stimulus-responsive chemo drugs were also intro-
duced to promote PDT treatment efficiency. Cui’s group
prepared a ROS responsive prodrug TL-CPT and established
a Ce6-CPT-UCNPs nanosystem for PDT and ROS-responsive
chemotherapy. In this study, Ce6 and TL-CPT were physically
loaded on the PEGylated UCNPs via a simple mixing and
ultrasonic treatment. Upon 980 nm laser excitation, the generated ROS by Ce6-CPT-UCNPs could cleave the thiol/ketal linker.
to release CPT, thereby forming dual-modal cancer therapy. The combined treatment can eliminate NCI-H460 lung cancers completely and no tumor recurrence was observed within 50 d. In another study, Oupický’s group reported hybrid PLGA/lipid nanoparticles with ICG and hypoxia-activated prodrug TPZ co-loaded for enhanced anticancer therapy.\[140\] Hypoxia caused by ICG-mediated PDT could subsequently activate the prodrug TPZ for antitumor activity. With iRGD peptide modified, this nanosystem could be significantly accumulated in cell monolayer and multicellular spheroids. In vivo studies demonstrated that the combination was capable of inhibiting primary tumor growth and metastasis effectively (Figure 9b).

4.4.2. PDT/PTT Dual-Modal Therapy

To date, most attempts have been made toward PDT treatment in association with PTT for dual-modal phototherapy. The distinctly superior synergistic effects of PDT and PTT attribute to the following aspects.\[141\] The local thermal induced by PTT can significantly accelerate blood flow in the tumor sites, which raises the level of oxygen and improve hypoxia condition for elevating efficacy of PDT. Meanwhile, oxygen-independent PTT effect could eliminate those surviving hypoxic cells in turn. To this end, diverse NIR-induced photothermal conversion nanomaterials act as a carrier for PS agents to combine PDT and PTT in one nanoplatform, such as graphene oxide,\[142\] gold nanostructures,\[143\] CuS nanomaterials,\[144\] poly(dopamine),\[145\] and so forth. Most of these works involve organic PS agents conjugated onto these nanoparticles via simple physical loading or covalent interactions. Liu’s group developed a UCNP@BSA-RB&IR825 nanocomplex by simultaneously loading RB molecules and IR825 dye (PTT agents) into BSA coating of UCNP@BSA nanomaterials to realize combined PDT and PTT.\[146\] Additionally, Sun et al. establish a core–satellite NR dimer-UCNP-Ce6 nanostructure based on gold NR dimer (core) and the Ce6-attached UCNPs (satellite) which were assembled through complementary base pairing (Figure 10a).\[147\] In this nanosystem, the NR dimer, which exhibited higher photo-thermal efficiency than the single NR, could serve as powerful PTT agents exposed to 808 nm laser. The PDT treatment can be realized indirectly through the UCNPs by irradiated of 980 nm laser. After irradiated by two NIR laser with a relatively low power density, NR dimer-UCNP-Ce6-mediated combined phototherapy was able to completely eliminate in vivo tumors without any regrowth. In these cases, the utilization of two different wavelength lasers for activating PDT and PTT will complicate the treatment process because of the obstacles in the precise alignment of the two laser beams.\[50b,148\] Therefore, many research groups, including ours, have made efforts to find new strategies to design one nanoplatform with single NIR light triggered phototherapy.\[149\] In our recent work, captoril-stabilized Au nanoclusters (Au125) were assembled onto mesoporous silica-coated UCNPs to form a new UCNPs@MS-Au125-PEG nanosystem (Figure 10b).\[150\] In this study, Au125 nanoparticles exhibited both intrinsic PDT effect and considerable PTT effect under 808 nm laser excitation. After that, we developed a novel nanoagent based on ICG-attached W18O49 nanostructure (WO@ICG) for 808 nm laser-induced synergistic PTT and PDT for enhanced antitumor efficacy (Figure 10c,d).\[152\] Hierarchical unique nanorod-bundled W18O49 nanostructure acted not only as an 808 nm light-induced photothermal agent, but also a potential nanocarrier for PSs (ICG) via physical interaction. Under single 808 nm laser irradiation, these WO@ICG nanostructures were capable to realize PDT/PTT dual-modal therapy. In vivo experiments validated that compared to PDT or PTT, WO@ICG-mediated synergistic phototherapy could achieve superior solid tumor growth inhibition with low dose.

4.4.3. Tri-Modal Synergistic Therapy

Based on the valid combined effects above, one single nanoplatform which can exert multimodal synergistic therapy was also developed for enhanced tumor-killing effect.\[152\] This treatment strategy always involves an elaborate nanosctructure for co-loading multiple components (chemo drugs, PSs, radiosensitizers, etc.) together. Thus rational design of a multifunctional nanoplatform to enable all these moieties exert their own effects is necessary. In 2014, Fan et al. first constructed a rattle-structured Gd-UCNPs core/mesoporous silica shell nanotheranostics (UCMSNs) for a cooperative tri-modal combination of chemo-/radio-/photodynamic therapy upon 980 nm laser irradiation and X-ray excitation.\[153\] In this system, HP (PS/radiosensitizer) was covalently grafted inside the silica shell, while Dtxl (chemo drugs/radiosensitizer) was encased into the inner cavity of UCMSNs. The tri-modal combined therapy was found to achieve remarkable in vivo tumor inhibition than the single treatment or their pairwise combination (Figure 11a). In our group, novel yolk-like GdO3:Ln@SiO2-ZnPc-DCs mesoporous microcapsules were developed via a mild and rational route for tri-modal synergistic therapy.\[154\] These multifunctional nanoplatforms were achieved by incorporating ZnPc PSs into GdO3:Ln@SiO2 and attaching carbon dots (NIR-triggered PTT agents) outside the SiO2 shell. Through loading anticancer drugs DOX into the hollow cavities between UCNPs core and SiO2 shell, these microcapsules were capable of realizing multimodal imaging guided multiple therapies (PDT, PTT, chemotherapy) in vivo. To avoid the possible early leak of drugs, we fabricated a pH/responsive P(NIPAm-MAA) polymer conjugated Y2O3:Yb,Er@Y2O3:Yb@mSiO2-Au25 nano-platform for excellent chemo-/photodynamic/photothermal therapy under 980 nm laser irradiation.\[155\] In this study, targeted and controllable release of DOX drugs were triggered by the thermal arising from the PTT effects and low pH in the cancer cells. When exposed to NIR irradiation, these multifunctional nanoplatforms led to improved tumor ablation in vivo (Figure 11b). Although there are many optional nanoplatforms for multiple therapies, such as biomimetic hybrid,\[156\] micellar nanomedicine,\[157\] simple and effective strategies for simultaneous synergistic phototherapy still need to be set up.

5. Antitumor Mechanism of NIR Light Triggered PDT

A comprehensive understanding of antitumor mechanism of PDT is crucial to further development of this field, although
it is complex and not fully understood. As known to all, three main mechanisms by which PDT mediates tumor destruction are now to be defined, namely direct tumor-cell killing, microvascular collapse, inflammatory and immune responses (Figure 12). In the first case, PS agents are preferentially taken up and retained by tumor cells, and induce direct cytotoxic effects on tumor cells in close proximity upon irradiation. This could be attributed to irreversible photodamage to important subcellular targets (e.g., plasma membrane, mitochondria) through oxidation of lipids, proteins and amino-acids by

Figure 10. a) Schematic illustration of DNA-based NR dimer and UCNP core–satellite assembly for multimodal imaging guided combination phototherapy. Reproduced with permission. Copyright 2015, Wiley-VCH. b) Schematic illustration for the formation of UCNPs@MS-Au25-PEG. Reproduced with permission. Copyright 2015, Wiley-VCH. c,d) Schematic illustration of the synthetic procedure of WO@ICG nanocomposites, and in vitro/in vivo combined phototherapy under 808 nm laser irradiation. Reproduced with permission.
ROS. In this point, the intracellular location of PS agents will determine primary site of photo-induced damage and critically influence the mode of cell death (e.g., necrosis, apoptosis or autophagy) following PDT.\textsuperscript{160} In another way, PDT effectively targets tumor-associated vasculature, therefore resulting in tumor infarction. Tumor growth depends on the nutrients and oxygen supplied by blood vessels. The activation of PS agents distributed in the vascular compartment via either passive or active targeting approaches are able to damage to the endothelial cells, leading to formation of thrombosis and consequently to vascular occlusion.\textsuperscript{164} As a consequence, vessel obstruction leads to local shortage of nutrients and oxygen, and triggers

**Figure 11.** a) Schematic illustration of the synthetic procedure of UCMSNs and their bioapplication for synergetic chemo-/radio-/photodynamic tri-modal therapy as well as magnetic/upconversion luminescent (MR/UCL) bimodal imaging upon NIR excitation ($\lambda = 980$ nm) and X-ray irradiation. Reproduced with permission.\textsuperscript{153} Copyright 2014, Elsevier. b,c) Schematic illustration for the formation of Y$_2$O$_3$:Yb,Er@Y$_2$O$_3$:Yb@mSiO$_2$-Au$_{25}$-P(NIPAm-MAA) and the imaging-guided synergistic multimodal anticancer therapy. Reproduced with permission.\textsuperscript{155} Copyright 2015, Elsevier.

**Figure 12.** The mechanism of action on tumors in photodynamic therapy.\textsuperscript{158} Copyright 2006, Nature Publishing Group.
secondary PDT related necrosis. In addition, PDT also produces an acute inflammatory response that attracts leukocytes (e.g., dendritic cell, neutrophils) to the treated region. During this stage, the inflammatory process is expressed by factors such as the secretion of cytokines, peroxidases, growth factors and other regulators. This in turn activates the host immune system to recognize, track down, and destroy tumor cells ultimately, which may show a long-term tumor control. In general, the antitumor outcome of PDT can be attributed to all these interrelated and/or inter-dependent biological mechanisms.

At the cellular level, two major molecular pathways regulating cell death have been well documented: death receptor-mediated (extrinsic) pathway, and mitochondria-mediated (intrinsic) pathway. For the extrinsic pathway, it involves the binding of death ligands and their cognate cell surface death receptors (e.g., fas ligand/fas receptor). After initiated by this event, signal transduction of death to protein fas associated death domain (FADD) happens, followed by the interaction with caspases. During the process of the latter pathway, release of cytochrome c and other apoptogenic molecules from mitochondrial into the cytosol plays an essential role, which could activate the caspases. It is believed that this release is controlled by proteins of the Bcl-2 family. In the end, both pathways would result in activation of caspase cascades such as caspase-3, -6 and -7 (Figure 13). This activation ultimately triggers a serial of biochemical process which execute apoptosis. Recently, increasing number of studies have reported to give evidence of the molecular mechanisms occurred in NIR-triggered PDT systems. For instance, our group revealed that NIR light triggered PDT-induced cytotoxicity resulted in cancer cell death through a mitochondria-involved apoptosis pathway by using UCNPs@TiO2 as PS agents. In this research, the generated ROS enabled to decrease mitochondrial membrane potential, which was involved with caspase reaction, such as releasing cytochrome c into the cytoplasm, and then activating caspase 3 to induce cell apoptosis. The in vivo studies also demonstrated that the regression in tumor growth was due to induction of apoptosis with up-regulated expression of caspase 3 protein. Ren and co-workers established a PDT nanosystem based on membrane-disruptive peptides Tat/Ha2 conjugated AuNR® pNIPAAm-Pc, and the predominant mode of cancer cell death via mitochondria-associated apoptotic pathway was also disclosed in this system. Upon the combined photoirradiation by 808 and 680 nm lights, this PDT system caused photodamage of the mitochondria by regulating Bcl-2 family proteins expression, and released cytochrome c to cytosol, which may lead to activation of caspase-9 and subsequently induce HeLa cell apoptosis. However, these subtle cell death mechanisms induced by NIR-triggered PDT could be mostly observed in vitro, since the in vivo situation is more complex.

6. Summary and Perspective
In summary, noninvasive PDT represents an effective and high selectivity tumor-ablative therapy as a future clinical intervention in oncology. By the virtue of light in the NIR window for biological tissue, NIR light excited PDT nanoplatform has gain more attention in treating numerous tumors at deep location. In this review, we have highlighted some exciting progress on
these PDT nanosystems, including the exploitation of PSs based on direct NIR excitation, and indirect NIR excited UCNPs-based PDT nanosystem. On top of that, with the application of nanotechnologies in PDT, advanced PDT nanoplatform with novel features, such as tumor-targeted or organelle-targeted ability, \( O_2 \) self-sufficient property, dual PSs-loaded capability, and PDT involved combined therapy, are discuss in detail. These well-designed nanoparticles-based PDT nanosystems here exhibit superior antitumor effects, and have made a big stride forward in resolving some problems associated with traditional PSs. However, there are still several considerable challenges facing in their translation into clinical practices.

(i) For PDT, ideal PS nanoagents are expected to possess great biocompatibility, good photostability, high extinction molar coefficient and high \( ^1O_2 \) quantum yield. In these days, diverse alternative PSs including organic PS molecules, inorganic NPs and UCNPs-based PSs, have been developed for NIR light induced PDT. For organic PSs, insufficient resistance to photobleaching is a crucial factor to limit their therapeutic performance. Furthermore, it is believed that their ROS yield could be improved via heave-atom effect. However, the toxicity of heavy metal ions remains a major concern for the application of those organic dyes in biological studies. New strategy to improve photoconversion performance of proven PSs is still fundamental for perfecting efficacy of PDT treatment. For UCNPs-based PSs via FRET mode, the key to achieve high ROS yield is the effective match between the absorption of PSs and the emission of UCNPs. In addition, the in vivo biocompatibility, biodistribution and long term toxicity of these PSs nanosystems also need to be systemically assessed before their clinical translation.

(ii) To engineer an optimal PDT nanosystem with advanced functions for thorough eradication of tumors is an active function of current research, such as specific targeting, improved tissue penetration, less oxygen-dependent properties, or combined therapy with different treatment mechanisms. On the one hand, researchers in this field gave a deep insight into different synthesis strategies and exquisite design of multifunctional PDT nanoplatforms. However, there is still a formidable challenge to obtain mass production of these nanosystems as a result of the complex synthetic process and formulations. Future studies on versatile and practical strategy to construct these delicate nanosystems suitable to clinical use are still required. On the other hand, a systematic study of the collaborative effects between PDT and different therapeutic modalities is crucial for further optimized therapeutic efficiency. This may be instructive to rational design of synergistic therapy nanosystems rather than randomly combined some therapeutic strategies together.

(iii) The parameters of NIR laser irradiation raise another important concern for NIR light induced phototherapy in biomedical application. In order to avoid unwanted photo-induced damage by the incident NIR laser, it is necessary to realize effective PDT process under the irradiation of light with safe dose. For instance, the employed excitation power density of 808 nm laser need to lower than conservative limit set for human skin exposure of \( \sim 0.33 \text{ W cm}^{-2} \).\textsuperscript{[166]} Besides, limited depth of treatment is still a difficult problem for PDT to treat tumors deeply located beneath the skin, even for NIR-excited PDT. Current research suggests that deep PDT is applicable to tumor located no more than 3 cm deeper under the skin, which is far from satisfactory for practical application. Hence, alternative different forms of delivering NIR light are needed. Recently, implanted NIR illumination device was proposed to address this limitation.\textsuperscript{[167]} This is of great meaning to explore whether these implantable NIR laser sources could achieve improved light-induced photodamage in deep-seated tumor.

(iv) There is an urgent need to establish preclinical tumor models for assessing the therapeutic index of deep PDT. In most current cases, in vivo performance of PDT nanoplatform is limited to subcutaneous tumor models on small rodent animals like mice. However, due to many human tumors are located inside the body and embedded beneath other tissues, these existing in vivo toxicology and therapeutic outcomes hardly meet the requirements of pre-clinical testing. Therefore in vivo studies should be supplemented and carried out on orthotopic tumor inside the body of mice, or even other big animals, which could expand the limits of existing experimental approach.

In the end, with the continuing dramatic advances in these significant fields, NIR excited PDT will become highly refined for treating numerous tumors at deep location. Though this will be a slow and tough process, we still believe that precise and individualized deep PDT treatment could be pushed finally from laboratory to clinic.

Acknowledgements
This project was financially supported by the National Natural Science Foundation of China (NSFC 51472233, 51672268, 51422209, 51332008, 51372243, 51572258, 51572257), the Major International Joint Research Project of NSFC (51720105015), NSFC for Overseas, Hong Kong & Macao Scholars Collaborated Research (51628201), National Basic Research Program of China (2014CB643803), Chinese Academy of Sciences (YZDY-SSW-JSC018), and Projects for Science and Technology Development Plan of Jilin Province (20170414003GH, 20160101300JC).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
near infrared light, photodynamic therapy, photosensitizers, targeted therapy, tumor hypoxia

Received: July 6, 2017
Revised: August 23, 2017
Published online:


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