Recent progress in nanophotosensitizers for advanced photodynamic therapy of cancer

Yamin Yang¹ and Hongjun Wang²,³

¹ Department of Biomedical Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing, Jiangsu 211106, People’s Republic of China
² Department of Biomedical Engineering, Stevens Institute of Technology, Hoboken, NJ 07030, United States of America
³ Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ 07030, United States of America

E-mail: yaminyang@nuaa.edu.cn and hongjun.wang@stevens.edu

Keywords: photodynamic therapy, nanophotosensitizer, intracellular delivery, tumour microenvironment, upconversion

Abstract
Owing to their unique photophysical and physicochemical properties, nanoscale photosensitizers (nano-PSs) comprising nanocarriers and molecular photosensitizers (PSs) have emerged as the practical solutions to circumvent current limitations in photodynamic therapy (PDT) of cancer. Nanosized materials have demonstrated their superiority either as the delivery vehicles for PSs to enhance the therapeutic efficacy in selective PDT or as the active participants to improve the energy conversion under a near-infrared light for deep tumour treatment. In this mini-review, we provide an overview of recent progress on nano-PSs for advanced PDT by elaborating three key elements in the photodynamic reaction, i.e. PS, oxygen, and light. Specifically, we discuss the state-of-the-art design of nano-PSs via the following strategies: (a) intracellular PS delivery based on hierarchical modifications, (b) stimuli-responsive nano-PSs targeting the tumour microenvironment, and (c) improved photophysical characteristics of nano-PSs as the energy transducers under deep tissue-penetrating light irradiation. In addition, the utilities of nano-PSs for combinatory therapy or for theragnostic purposes were also discussed. In the end, the current challenges and future perspectives of nano-PSs towards clinical translation were also highlighted along with the concluding remarks.

1. Introduction
Photodynamic therapy (PDT) is a two-stage treatment that involves the administration of a photosensitizer (PS), followed by the activation with appropriate light irradiation to generate the cytotoxic reactive oxygen species (ROS) for cell killing. Figure 1 illustrates the established mechanism of photodynamic reaction to produce ROS or singlet oxygen (¹O₂) through both type I and type II pathways [1]. Owing to the intrinsic tumour selectivity of PSs and possible co-localization of illuminating light to the tumour lesions, PDT is considered as a promising tumour intervention modality with minimum long-term side effects [2]. To date, the Food and Drug Administration has approved the use of porfimer sodium (Photofrin®) and meta-tetrakis(3-hydroxyphenyl) chlorin (Foscan®) as PSs for PDT treatment of oesophageal cancer, non-small cell lung cancer, and precancerous changes of Barrett’s oesophagus [3, 4].

Typically, the PSs can be small organic molecules with tetrapyrrole structures, such as porphyrins, chlorins, derivatives of phthalocyanines with the incorporation of Zn or Al into the phthalocyanine macrocycle (e.g. zinc phthalocyanines, ZnPc₄; chloro aluminium sulphonated phthalocyanine, AlPcS), natural products (e.g. hypericin, riboflavin), or indocyanine dyes (e.g. indocyanine green, ICG) [5, 6]. However, the small organic PSs are often hydrophobic in nature with poor solubility, limited retention, rapid clearance, and a relative low molar absorption coefficient with the tissue-penetrating light. Meanwhile, these PSs tend to aggregate under the physiological conditions, significantly reducing the quantum yields of ROS production and photodynamic activity [7, 8]. As a consequence, high concentrations of PSs and light dosage must be delivered to the tumours for a sufficient therapeutic efficacy, which may cause unwanted side effects.
Figure 1. Schematic illustration of PDT mechanism. PS can be activated from a ground state to an excited singlet state ($^1$PS$^*$) following one (hν) or two-photon (2hν) excitation and then relax to an excited triplet state ($^3$PS$^*$). This triplet PS can interact with molecular oxygen and generate ROS in the forms of superoxide anion radicals (O$_2$$^-•$), hydroxyl radicals ($•$OH), and hydrogen peroxide (H$_2$O$_2$) through type I mechanism or induce singlet oxygen ($^1$O$_2$) generation via energy transfer through type II mechanism.

To this end, substantial efforts have recently been made to develop novel categories of PSs with optimal attributes, such as synthetic phenothiazinium, boron-dipyrromethene (BODIPY), and aggregation-induced emission dyes [5, 6, 9]. With their compelling advantages, nanoscale PSs (nano-PSs) have emerged as an effective alternative to partially if not fully incorporate three essential elements of photodynamic reaction, i.e. PS, oxygen, and light [10, 11]. The research on nanotechnology-assisted PDT continues to evolve quickly, with frequent reports on novel materials and innovative techniques in recent years [10–13]. Chen et al. overviewed various nanomaterial-based platforms for enhanced PDT from a material perspective and provided a clear framework of the up-to-date development of four generations of PSs [14]. One recent comprehensive review by Yang et al., on the other hand, emphasized on the employment of different physicochemical approaches, including light, magnetic fields, microwave, ultrasound, and x-rays, towards the transition of PDT into the medical domain [15].

In this short review, we discussed the recent progress in designing versatile nano-PSs for advanced PDT with a particular focus on the following state-of-the-art approaches: (a) enhanced PS delivery efficacy for selective PDT via intracellular targeting, (b) stimuli-responsive nano-PSs targeting the hypoxia tumour microenvironment, and (c) improved photophysical characteristics of nano-PSs under the deep tissue-penetrating light irradiation. Figure 2 shows some representative nanostructures employed in PDT with demonstrated functional advantages, such as efficient PS delivery, specific PS accumulation in tumours, and near-infrared (NIR) light-excited nano-PSs for deep PDT, etc.

2. General advantages of nano-PSs for PDT

Nanomaterials have been generally regarded as drug delivery vehicles to provide enhanced aqueous stability and controlled release attributes. Incorporation of hydrophobic PSs into nanomaterials has been extensively explored to increase PS payloads and prevent aggregation. By selecting appropriate nanomaterials, PSs can be protected from direct exposure to external interferences without compromising their photophysical properties [12, 16, 17]. Various nanocarrier platforms, including liposomes [18, 19], micelles [20, 21], dendrimers [22, 23], polymeric nanoparticles [24, 25], mesoporous silica [26, 27], gold nanostructures [28–30], and other metallic nanomaterials [31], have been used to encapsulate or conjugate PSs. PS loading in the vehicular nanocarriers can be achieved by noncovalent methodologies using self-assembly, interfacial deposition, core–shell entrapment, electrostatic interaction, physical adsorption, or covalent processes via chemical immobilization [13]. The nano-PSs can be further modified using hydrophilic functional groups, such as polyethylene glycol (PEG) [32], hyaluronic acid [33], or cell membrane [34], to achieve a steric exclusion activity (‘stealth effect’) and to increase circulation time in the body after administration [35].

3. Conventional targeting strategies of nano-PSs for PDT

Selective delivery of PS molecules to malignant cells has involved the particle design using versatile approaches to enhance tissue penetration, tumour specific accumulation, and cellular internalization of PSs. By virtue of their nanosize, traditional tumour targeting strategies of nanomedicine include enhanced permeability and retention (EPR) effect-based passive targeting and active targeting by grafting ligands onto the nanocarrier surfaces. For passive targeting, nano-PSs can diffuse through the permeable tumour
vasculature and impaired lymphatic drainage system, and retain preferentially in the solid tumours [36, 37]. Nano-sized carriers with large surface-to-volume ratio can also serve as superior vehicles for long-sustained and selective delivery of PSs to tumour cells by conjugating versatile targeting moieties, such as antibodies [38], proteins [39], peptides [40], folate [41], biotin [42], aptamers [43], and other small molecules, which bind to specific receptors over-expressed on the tumour cells, including cancer-associated receptors, folic acid receptors, epidermal growth factor receptor, and transferrin receptor [44–46].

4. Intracellular targeting nano-PSs for advanced PDT

In contrast to chemotherapy, the key cytotoxic molecule during PDT, i.e. $^1\text{O}_2$, has a very short lifetime, which leads to a very limited diffusion distance (radius of action of $^1\text{O}_2$ is <20 nm) [1, 47]. Therefore, not only the distribution and accumulation of PSs in the tumour tissues is crucial, but the localization and penetration of PSs into subcellular compartments is also of great essence for a satisfactory efficacy of PDT. Subcellular organelles, such as mitochondria [48], lysosomes [49], plasma membrane [50], endoplasmic reticulum [51], and nuclei [52], have been regarded as the potential therapeutic targets of PDT.

In our previous review [53], we summarized the recent advances in developing subcellular targeting gold nanomaterials with the capabilities of cellular penetration and endosomal escape via various surface modifications or physical injection approaches. Similarly, hierarchical targeting strategies have been proposed for an efficient nano-PS intracellular delivery system to achieve an idealized scheme, including cell-specific targeting with an internalizable ligand and subcellular targeting signal with endosomolytic activity [54, 55]. In table 1, we summarized the representative targeting strategies to specifically deliver nano-PSs to subcellular compartments for enhanced PDT.

4.1. Mitochondrial targeting nano-PSs

Mitochondria are crucial regulators of stress responses, apoptosis, and diverse cellular signal transduction pathways. In the case of PDT, mitochondria are known as the sensitive repository for ROS production. It is noted that mitochondria are polarized as the negative electric potential differences between outer and inner membranes with the lipid bilayer structure. Nano-PSs with positive charge may have a high tendency to localize in the mitochondria by potential-driven translocation upon their entry into the cells. Some of clinically approved PSs do show their capability of partial localization to the mitochondria [64], further endeavours are pursued to further enhance mitochondria-accumulation efficiency of PSs, including conjugation of positively charged lipophilic moieties or mitochondrial targeting sequences onto the nanocarriers [65–67].
Table 1. Representative targeting strategies of nano-PSs for enhanced PDT.

| Nanoplatform                               | PS          | Subcellular target | Functional modification | Ref. |
|--------------------------------------------|-------------|--------------------|-------------------------|------|
| TiO$_2$-coated UCNPs                       | TiO$_2$     | Mitochondria       | TPP                     | [56] |
| Mesoporous silica nanoparticles            | Ce6         | Mitochondria       | TPP                     | [57] |
| Au nanoparticles                           | 5-ALA       | Mitochondria       | TPP                     | [58] |
| Au@Pt nanoparticles                        | Ce6         | Mitochondria       | Folic acid, PEG         | [59] |
| Mesoporous silica nanoparticles            | Ce6         | Nucleus            | TAR and RGD peptide    | [60] |
| 2,3-Dimethylmaleic anhydride nano-composites | PpIX       | Nucleus            | NLS peptide            | [37] |
| DSPE-mPEG5000                              | BODIPY      | Lysosome           | Acid-sensitive dimethyl-aminophenyl group | [61] |
| Ruthenium and carbon-doped TiO$_2$ nanoparticles | Ruthenium and TiO$_2$ | Lysosome          | Folic acid, morpholine-directed groups | [62] |
| Self-assembled Ru–Pt metallacage           | Ruthenium   | Lysosome           | Amphiphilic polymer     | [63] |

For instance, the triphenylphosphonium (TPP)-based mitochondrial targeting strategy was employed by Li group to deliver TiO$_2$-coated upconversion nanoparticles (UCNPs) [56] and chlorin e6 (Ce6)-conjugated-mesoporous silica nanoparticles [57] to the mitochondria, where activated TiO$_2$ and Ce6 could boost local ROS generation, leading to mitochondrial collapse and irreversible cell apoptosis.

In our previous study [58], we also conjugated the mitochondria-targeting TPP groups with quaternary ammonium cations onto the gold nanoparticle surface for selective delivery of 5-aminolevulinic acid, the precursor of natural PS of protoporphyrin IX (PpIX), to the mitochondria of human breast cancer cells. The modified nano-PSs released from the endocytic vesicles, trafficked to the mitochondria, and elevated ROS formation upon light irradiation, leading to significantly enhanced therapeutic efficacy of PDT. Following a hierarchical targeting strategy, Song et al designed the mesoporous Au@Pt-PEG-Ce6 NPs structures for selective delivery of Ce6 to MCF-7 cells in combination of PDT with photothermal therapy (PTT) [59]. The Au@Pt nanoparticles were labelled with folic acid for cancer cell internalization, and modified with TPP for mitochondria-targeting. Significant improvement of the cell killing efficacy was seen as a result of enhanced cellular uptake, effective mitochondrial ROS burst, and thermal destruction. The cell viability was 46.2% after 150 s irradiation using an 808 nm laser (1.2 W cm$^{-2}$), and then significantly decreased to 13% upon a combination of 660/808 nm laser irradiation.

4.2. Nucleus targeting nano-PSs

Cell nucleus is the central regulator of cell proliferation, metabolism, gene activation, and cell cycle management; therefore, it is also a desirable target of various therapeutics, including PDT. It is anticipated that intra-nuclear transport of PSs can increase the photocytotoxicity due to ROS generation in close vicinity to the nucleus for enhanced DNA damage [52]. Cell-penetrating peptides (CPPs) or nuclear localization sequence (NLS) with nucleus homing capabilities are often used to modify the drug delivery system for translocation into the nucleus [68]. Typical CPPs include trans-activating transcriptional activator (TAT) and arginylglycylaspartic acid (RGD) peptide. NLS consisting of a chain of positively charged amino acids can interact with the integral membrane protein family receptors on the nucleus and trigger the receptor-mediated nuclear importing [69–71].

Shi group has reported a series of studies designing cancer cell nucleus-targeting nanocomposites for advanced tumour therapeutics [52]. In one study, mesoporous silica nanoparticles co-conjugated with nucleus-targeting sequence TAT and RGD were used as carriers to deliver PS Ce6 to the nuclei of HeLa cancer xenografts, resulting in oxidative damage of the DNA helix under an extremely low light dose [60]. Less than 40% cancerous cells survived after PDT treatment under as low as 5 mW cm$^{-2}$ irradiation for 5 min. For the hierarchy targeting, Han et al constructed the nanocomposites consisted of pH-responsive 2,3-dimethylmaleic anhydride (DMA) conjugated with NLS peptide and loaded with alkylated PpIX as the PS. The nano-PSs underwent the charge reversal in response to the acidic tumour microenvironment and penetrated the tumour cells based on the electrostatic interactions. The NLS sequence further guided PSs to the cell nucleus, thus achieving improved and selective PDT [37].

4.3. Lysosome targeting nano-PSs

Lysosomes are involved in important cellular processes via mediation of the macromolecule degradation. Lysosomes also play an essential role in intracellular trafficking of nanomaterials via endocytosis, and are considered as the major compartments for nanomaterial accumulation [72]. Although lysosomes are much less preferred as the intracellular targets of photooxidation in comparison to mitochondria and nucleus, the significant acid interior (pH 4.5–5.0) of lysosome could serve as a potential site for pH-responsive PSs [73].
Figure 3. Schematic representation of nanoplatforms (Ru-NO@FA@C-TiO$_2$ NPs) for lysosome-targeting PDT. The nanoparticles selectively accumulated in the lysosomes of HeLa cells. The direct attack on lysosomes by NO and ROS resulted in significant cell killing under NIR light irradiation. Adapted with permission from [62]. Copyright 2015 The Royal Society of Chemistry.

In one example, Hu et al incorporated the acid-sensitive dimethylaminophenyl group in the NIR-absorptive BODIPY PS core and then encapsulated within the amphiphilic DSPE-mPEG5000 via precipitation, affording the water-soluble nano-PSs. Coupling with the high-selectivity enabled by acidic lysosomes, the viability of A549 cancer cells incubated with lysosome-targeting BODIPY NPs was dramatically reduced after acid-activatable PDT under the NIR light [61]. As shown in figure 3, Xiang et al developed a nanoplatform composed of a ruthenium nitrosyl donor (Lyso-Ru-NO) and the carbon-doped titanium dioxide nanoparticles for cancer cell and lysosome dual-targeting. Incorporation with folic acid and morpholine-directing groups rendered its capability of targeting folate-receptor overexpressing-cancer cells and specific accumulation in the subcellular lysosomal organelles, where NO and ROS were simultaneously released upon 808 nm light irradiation. Such a lysosome-targeting nanoplatform showed the highest anticancer efficacy compared to the nontargeted counterparts under NIR light sensitization [62].

Due to the close relationship between lysosomes and apoptosis/necrosis, lysosome-localized PSs are also more effective in directly inducing photodamage on lysosomes and lead to subsequent cell death. Zhou et al found that the self-assembled Ru–Pt metallacage encapsulated within an amphiphilic polymer selectively accumulated in the lysosomes and the production of $^1$O$_2$ within lysosomes induced lysosomal disruption under two-photon NIR light irradiation, which resulted in a high phototoxicity to tumour cells [63].

5. Tumour-microenvironment targeting nano-PSs

Compared to healthy tissues, it is well established that the tumour microenvironment has unique physiological characteristics such as hypoxia, acidosis, vascular abnormalities, and up-regulation of certain enzymes [74].

The strategy of targeting the corresponding aspects of tumour microenvironment would offer much broader application potentials to better address the tumour heterogeneity than merely targeting tumour-specific receptors. Increasing attention has been given to exploit the stimuli-triggered activation of nano-PSs in response to endogenous hypoxia and acidic pH once they extravasate into the tumour microenvironment [75]. We listed several representative nano-PSs (table 2) that achieved the enhanced PDT antitumor efficiency by targeting the hypoxia or/and acid tumour microenvironment.

5.1. Hypoxia targeting nano-PSs

Scant oxygen supply has been recognized as one of the hostile hallmarks of solid tumours from the increased oxygen consumption during the metabolic activities of proliferating carcinoma cells [78]. In the meantime, PDT is an oxygen-dependent process where ROS production greatly relies on the availability of oxygen. Thus, hypoxia in the tumour microenvironment is closely related to the increased metastasis, poor prognosis, and resistance to chemotherapy, and insufficient oxygen in the tumour tissues would also impair the PDT efficacy. Moreover, along with the progress of PDT, the hypoxic tumour microenvironment is further exacerbated by continuous oxygen depletion and vice versa.
There was a release of IR780 specifically disrupting mitochondrial respiration due to its natural self-generating oxygen. MSNs@IR780 nanocomposites were prepared to scavenge the hypoxic tumor microenvironment by accumulation by modifying with the TAT peptide (figure 31). The surface coronae group of 2,3-dimethylmaleic anhydride (DMA) protected the CPP via an acid-labile amide bond to prolong the circulation time while achieving acid-activated tumor penetration. This O2 nanoparticle can decompose H2O2 into O2 and sustainably generate oxygen under H2O2-rich physiological conditions. In a recent study reported by Yang et al, a Mn3O4 nanocomposite was prepared to scavenge the hypoxic tumor microenvironment by self-generating oxygen [78]. The PS IR780 was absorbed into the mesoporous silica nanoparticles (~90 nm in diameter) and then the surface pores were capped with 5 nm Mn3O4 nanoparticles, which could catalyse H2O2 into O2 and thus ameliorate the hypoxic microenvironment in an MKN-45P tumor xenograft model. The release of IR780 specifically destructed the respiration of the mitochondria due to its natural mitochondrial affinity and efficiently killed MKN-45P cancer cells upon 808-nm laser irradiation (1 W cm−2, 5 min) in both in vitro and in vivo conditions (figure 5).

Recently, we also developed a bimetallic and biphasic rhodium (Rh) and Au porous core–shell nanosystem (Au@Rh-ICG-CM) to address tumor hypoxia while achieving bimodal imaging-guided high PDT efficacy (figure 6) [31]. Such porous Au@Rh core–shell nanostructures exhibited catalase-like activity to achieve antitumor outcomes through cancer starvation [82]. For the first approach, nanocarriers have demonstrated their capability of alleviating tumor hypoxia and boosting PDT via delivery of a high concentration of molecular O2 or in situ O2 generation by catalysing the decomposition of endogenous hydrogen peroxide (H2O2) [83]. Qian et al reviewed the recent trend in modulation and utilization of tumor hypoxia via nanomedicine-based strategies to improve PDT [82]. Yang et al also summarized the design and application guideline of various H2O2-responsive nanomaterials with oxygen-self-generation capacity to target the hypoxia tumor microenvironment for enhanced PDT [84]. For instance, Liu et al designed a nanocomposite (O2@DANPCE6+PFOB) to alleviate tumor hypoxia by incorporating perfluoroxyctyl moieties (perfluoroxyctyl bromide, PFOB) as O2 carriers and to enhance the tumor cell accumulation by modifying with the TAT peptide (figure 4). The surface corona group of 2,3-dimethylmaleic anhydride (DMA) protected the CPP via an acid-labile amide bond to prolong the circulation time while achieving acid-activated tumor penetration. This O2 self-supplemented nanoplatform co-loaded with Ce6 exhibited a potent inhibition of tumor growth compared to traditional PDT as observed in both in vitro cytotoxicity and in vivo anti-tumor study on 4T1 tumor-bearing mice after intravenous injection and 10 min 660 nm laser (0.5 W cm−2) irradiation [76]. Ping et al reported a design of nano-PSs composed of a hybrid perfluorosiloxane-polystyrene particle core doped with a fluorinated PS and a biocompatible poly-L-lysine shell [77].

Because of the O2-carrying capability of intra-particle ‘F-C’ bonds, the fluorinated nano-PSs saturated with O2 exhibited approximately 3.5 folds more 18O2 production yield and a higher in vitro PDT efficiency. Manganese dioxide (MnO2) and Mn3O4 nanoparticles could decompose H2O2 and sustainably generate oxygen under H2O2-rich physiological conditions. In a recent study reported by Yang et al, a Mn3O4@MSNs@IR780 nanocomposite was prepared to scavenge the hypoxic tumor microenvironment by self-generating oxygen [78]. The PS IR780 was absorbed into the mesoporous silica nanoparticles (~90 nm in diameter) and then the surface pores were capped with 5 nm Mn3O4 nanoparticles, which could catalyse H2O2 into O2 and thus ameliorate the hypoxic microenvironment in an MKN-45P tumor xenograft model. The release of IR780 specifically destructed the respiration of the mitochondria due to its natural mitochondrial affinity and efficiently killed MKN-45P cancer cells upon 808-nm laser irradiation (1 W cm−2, 5 min) in both in vitro and in vivo conditions (figure 5).
Figure 4. Schematic illustration of O₂@DANPCe6+ PFOB mediated oxygen-replenishing PDT. PFOB as O₂ carriers to oxygenate hypoxia tumour tissue during PDT. The protective DA corona will detach from the particle surface at the tumoural acidic microenvironment and the TAT peptide will facilitate its tumour-penetrating ability, leading to an enhanced therapeutic efficacy in both 4T1 cells in vitro and 4T1 tumour-bearing mice in vivo. Adapted with permission from [76]. Copyright 2019 The Royal Society of Chemistry.

Figure 5. Schematic diagram shows the H₂O₂-triggered release of IR780 and O₂ of Mn₃O₄@MSNs@IR780, resulting in significant decrease of tumour size and weight after in vivo PDT. Adapted from [78]. CC BY 4.0.

efficiently catalyse oxygen generation from endogenous H₂O₂ in tumours. After coating with tumour cell membrane (CM), the PS ICG could be loaded and retained in the cavity of Au@Rh-CM. Both in vitro and in vivo results demonstrated that Au@Rh-ICG-CM was able to convert endogenous H₂O₂ into oxygen and then elevated the production of tumour-toxic ^1O₂, significantly enhancing the fluorescence and photoacoustic imaging-guided PDT.
5.2. pH-responsive nano-PSs

As tumour cells rely heavily on the glycolysis for energy consumption rather than the oxidative phosphorylation, leading to a higher level of extracellular lactic acid, thus, the pH of the tumour microenvironment is more acidic (6.5–6.8) than that of healthy tissues. pH-responsive PS delivery systems have also been investigated for PDT. These nanostructures are usually grafted with reactive linkages, which are cleavable upon pH stimuli and then undergo PS release. Li et al fabricated a tumour-pH-responsive supramolecular PS structure based on the electrostatic interaction between negatively charged octasulfonate-modified zinc(II) phthalocyanine (ZnPcS8) and cationic layers of double hydroxide, which could be efficiently activated in the acidic tumour microenvironment (pH 6.5), resulting in 95.3% tumour growth inhibition with minimal skin phototoxicity [80]. Hu et al synthesized the pH-sensitive nanoparticles instead of harnessing tumour hypoxia, the combination of PDT with other hypoxia-responsive chemical moieties or cancer starvation therapeutic agents can collaboratively achieve the synergistic anticancer efficiency. For example, PDT-induced hypoxia would fully activate the hypoxia-responsive prodrug and severely damage the tumour blood vessels in a PDT-aggravated hypoxic condition. By incorporating the hypoxia-sensitive nitroimidazole molecules, Qian et al encapsulated the widely-used chemotherapeutic drug doxorubicin (DOX) in 2-nitroimidazole-grafted conjugated polymer to achieve a synergistic treatment with PDT and chemotherapy [85]. The nanocarrier complex could generate ROS after light-triggered stimulus and subsequently induce hypoxia to release DOX upon nanocomposite disassembly, which provided an innovative design guideline for drug delivery using programmed stimuli-responsive triggers. Noted that tirapazamine (TPZ), an aromatic N-oxide, has 300-fold higher toxicity under anoxic conditions than aerobic conditions, Liu et al designed an Hf-porphyrin metal-organic framework platform with high porphyrin and TPZ loading capacity [79]. Depletion of oxygen during PDT aggravated the hypoxic environment of tumours and further activated TPZ to enhance the treatment efficacy.

Instead of harnessing tumour hypoxia, the combination of PDT with other hypoxia-responsive chemical moieties or cancer starvation therapeutic agents can collaboratively achieve the synergistic anticancer efficiency. For example, PDT-induced hypoxia would fully activate the hypoxia-responsive prodrug and severely damage the tumour blood vessels in a PDT-aggravated hypoxic condition.
Figure 7. (a) Schematic illustration of the penetration depth of different wavelengths in human tissues. (b) Simplified energy transfer photon upconversion process. A sensitizer first absorbs a photon and is promoted to its excited state, promoting the emitter to the intermediate excited state. A second sensitizer then absorbs a photon and promotes the excited emitter to the higher-lying state. The excited emitter then relaxes back to the ground state and activates PS by releasing higher energy photons. (c) FRET-based PS activation mechanism via nonradiative transition. When the PS molecule is within a certain distance (Förster distance <10 nm) with the donor molecule, the excited donor can experience the transfer of nonradiative energy to activate the PS molecule.

of acetylated β-cyclodextrin (Ac-β-CD) using oil-in-water emulsion technique and then modified with gelation-folic acid ester for cancer targeting [81]. This nanodevice was further loaded with an anticancer drug camptothecin and a PS phthalocyanine (PcZn) to improve the synergistic outcomes of chemo-PDT.

6. Nano-PSs for deep PDT

Current PS molecules (e.g. chlorin, ZnPc4, porphyrin, and texaphyrin) generally require ultraviolet (UV) or visible light for efficient activation upon one-photon excitation. Due to light scattering and absorbance by biological tissues, UV or visible light of high energy with limited tissue penetration hardly reaches deep tumour sites or inner cores of large solid tumours, which remains the major obstacle for current PDT. Figure 7(a) shows the tissue penetration depth of light with varying wavelengths, where NIR (650–1350 nm) is a favourable range for in vivo applications with efficient luminous flux yet minimal auto-fluorescence in its spectral region. Some PSs such as ICG (810 nm) and aluminium sulfophthalocyanine (790 nm) can absorb NIR light with deeper tissue penetration but are considered less effective than traditional PSs considering the low yield of the triplet state upon irradiation. In this regard, upconversion (UC), two-photon activation, and self-illumination-based strategies have been developed with the advances of nanotechnology to circumvent the limitations of current PDT and expand its applicability for deep tumour treatment [86].

6.1. Upconversion PDT

Photon UC is known as a nonlinear optical phenomenon that can convert a lower energy excitation to a higher energy emission through an anti-Stokes process. Nanoparticles with controllable upconverted emission properties can absorb more than two low-energy photons of the NIR region in a cascade manner and then efficiently convert them into a higher-energy photon in the visible or UV region. Figure 7(b) illustrated the simplified process during photon UC for PS activation based on the energy transfer mechanism. UCNPs can be used as energy donors to activate PS for cytotoxic ROS production through electronic excitation based on either radiative (luminescence) or non-radiative (Förster resonance energy transfer, FRET) energy transfer. The primary mechanism of FRET-based energy transfer for PS activation was shown in figure 7(c).

As photon UC typically occurs between two different types of rare-earth ions, UCNPs are usually comprised of an appropriate host lattice, such as fluorides NaYF4, NaGdF4, NaLuF4, and BaYF5, doped with transition metal, actinide or lanthanide ions (Yb3+/Er3+/Tm3+) [87]. So far, many PSs, such as porphyrin derivatives, ZnPc4, Ce6, methylene blue, and rhodamine B, have been used in a synergistic combination with UCNPs to augment efficient ¹O₂ generation under NIR light irradiation. Hamblin recently summarized up-to-date research works of UCNPs for the use in PDT with a wide range of different PSs [88]. For efficient energy transfer, the UCNP emission wavelength should match the absorption of entrapped PS, and the PS should be in close proximity to the luminous inner core of UCNPs. The entrapment of PSs in UCNPs can be achieved through covalent conjugation, physical adsorption, or silica encapsulation, dependent on the hydrophobicity of PSs. Similar to the above-mentioned nano-PSs, UCNPs can be modified with hydrophilic supports and further functionalized with targeting moieties to enhance their selective accumulation at the tumour site.
Gnanasammandhan et al employed the mesoporous-silica-coated UCNPs (NaYF4:Yb3+/Er3+) to convert deeply penetrating NIR light at 980 nm to activate two Ps (MC-540 and ZnPc) simultaneously for enhanced PDT [89]. In vivo studies showed the promising tumour growth inhibition in PDT-treated mice upon intratumor injection or intravenous injection. However, while the porous structures are beneficial for oxygen and ROS diffusion, leakage of Ps during systemic circulation may lead to inadequate dosing of Ps in the targeted site. Yuan et al conjugated DOX with PEGylated polyelectrolyte through a UV-cleavable ortho-nitrobenzyl linker and used this structure as the matrix for UCNPs (NaYF4:Yb3+/Tm3+) encapsulation [90]. This NIR light-regulated UCNPs©DOX structure could photocleave the linker for controlled release of DOX upon 980 nm laser irradiation and activate Ce6 to produce ROS at a high efficiency.

Ongoing researches have focused on further enhancing the UC quantum yield of UCNPs and optimizing FRET efficiency between Ps and UCNPs based on intensive investigations on the underlying mechanism. In particular, the amount of PS loading and the distance control between UCNPs core and attached PS molecules should be optimized when designing the UCNPs-PS system for maximum PDT effect.

6.2. Two-photon PDT

Two-photon excitation takes place with simultaneous absorption of two photons. Similar to the UC process, two-photon PDT is characterized by nonlinear absorption of two low-energy photons of NIR light with the resulting emission of high-energy visible light to activate Ps [91]. The main difference between UC process and two-photon-induced PS excitation is that the light frequency conversion efficiency during UC is orders of magnitude higher than that of a nonlinear two-photon absorption mechanism. The two-photon absorption process requires excitation at a high density of \( \sim 10^6 \) W cm\(^{-2} \) by an ultra-short pulsed (e.g. femtosecond) laser, while NIR light UC can be achieved with an excitation density of 10–100 W cm\(^{-2} \) provided by a low energy continuous-wave diode laser [92].

To increase the efficiency of two-photon PDT, large two-photon cross-sections are desirable, which have been obtained with symmetrically or dissymmetrically \( \pi \)-extended porphyrins, and supramolecular assemblies [93]. Different nanosystems have been designed to expand the two-photon cross-sections of Ps based on the FRET mechanism [94].

Duan et al conjugated two-photon light-harvesting hydrophobic polymer to tetraphenylporphyrin (TPP) and a red-emitting imaging dye (TPD) and found that the two-photon emission of tetraphenylporphyrin and TPD was enhanced up to \( \sim 161 \) and \( \sim 23 \) times, respectively [95]. These nanostructures were further modified with folic acid groups and remarkably improved the PDT efficiency up to about 149 times with selective targeting of cancer. In a recent study, Karges et al reported the design of Ru(II) polypryidine complexes with (E,E’)-4,4’-bisstyryl-2,2’-bipyridine ligands and a red-shifted one photon and strong two-photon absorption using an in silico optimization [96]. In vivo studies confirmed that the compounds could eradicate a multi-resistant tumour on a mouse model upon clinically relevant one-photon (500 nm) and two-photon (800 nm) excitation.

The relatively low two-photon absorption efficiency and low \( ^1O_2 \) quantum yield remain as the major concerns of conventional Ps for two-photon PDT. Clearly, materials exhibiting a long triplet-exciton emission are more favourable to extend the energy transfer to surrounding \( O_2 \) for enhanced generation of cytotoxic \( ^1O_2 \). Recently, various strategies have been explored to achieve a longer excited triplet state lifetime and to increase the efficiency of light energy transfer in the design of photosensitive materials [15, 97]. For example, the long-lived room temperature phosphorescence materials have attracted increasing attention for PDT applications [98]. Yang group confirmed that space-confined and interface-confined microenvironments of 2D matrix would facilitate ultralong-lived triplet exciton with second-scale lifetimes, which was significantly longer than that of conventional Ps in microsecond to millisecond range [99]. As shown in figure 8, they also developed a nanohybrid system through the assembly of different aromatic acids within the layered double hydroxide nanosheets for two-photon-induced \(^1O_2 \) generation. The quantum yield of \(^1O_2 \) was greater than most as-reported Ps to date and led to dramatical tumour ablation in vivo under the 808 nm laser irradiation [100].

6.3. Self-illuminated PDT

Luminescent materials (or phosphors) or luminescent proteins (such as luciferase and horseradish peroxidase) can emit chemiluminescence or bioluminescence after an external excitation source is removed. The self-illuminating luminescent materials can serve as an internal light source for flourishing PDT in deep tissue treatment, and their afterglow properties are particularly attractive for continuous PDT, since they can continuously excite the nearby Ps even after the stoppage of excitation. Persistent luminescence nanoparticles are a newly emerging class of functional optical biomaterials in PDT. Fritzen et al reviewed the up-to-date literatures on their applications in luminescence imaging and PDT [101].
Figure 8. Schematic representation of the nanohybrids composed of layered double hydroxide nanosheets and five aromatic room temperature phosphorescence materials as two-photon PSs for $^{1}\text{O}_2$ generation. The viability of HeLa cells and in vivo tumour growth were significantly inhibited by the nanohybrids under an 808 nm NIR laser irradiation. Adapted from [100]. CC BY 4.0.

Figure 9. Schematic illustration of self-assembly of the luminoland Ce6 conjugate into a core–shell nanoparticle for in vivo luminescence imaging of the colitis development in mice and for in vivo antitumor PDT. Through the bioluminescence resonance energy transfer, the luminescence originating from luminol upon triggering can excite Ce6 to produce fluorescence and $^{1}\text{O}_2$. Adapted from [105]. CC BY 4.0.

In one example reported by Wang et al, they fabricated the phosphorescent Cr3+, Yb3+, Er3+ triple-doped zinc gallogermanate nanostructures, which were coated with mesoporous silica for the loading of AlPcS. The as-prepared nanoparticles exhibited long-lasting persistent luminescence and remarkable afterglow properties under fractionated light irradiation which triggered the generation of a large amount of $^{1}\text{O}_2$ and enhanced tumour destruction [102].

In another recent review, major types of persistent luminescence nanoparticles and their multiple biomedical applications were summarized, in which controllable synthesis methods were considered as the current technical challenges to achieve the optimal optical properties [103]. In recognition of the decrease of luminescence performance and low utilization efficiency of traditional persistent luminescence materials, Sun et al recently tried to prevent the mass loss and maintained the intact crystal lattices of persistent luminescence materials by homogeneously dispersing high temperature-sintered persistent luminescence materials into the alginate-Ca$^{2+}$ hydrogel. Owing to the retained NIR luminescence and red-light renewability, the hydrogel composites could sensitize continuous generation of $^{1}\text{O}_2$ after injection into the tumour site, favouring repeated PDT [104].

Luminol is another extensively studied luminescent donor. As shown in figure 9, Xu et al developed an amphiphilic polymer conjugated with luminol and Ce6 that could self-assemble into a nanoparticle for in vivo luminescence imaging and PDT in deep tissues. Higher level of ROS and myeloperoxidase generated
Table 3. Multifunctional nano-PSs for combinational and theragnostic PDT.

| Nanoplatform                        | PS                  | Functional group               | Light source | Applications and remarks                                                                 | Ref. |
|-------------------------------------|---------------------|--------------------------------|--------------|------------------------------------------------------------------------------------------|------|
| UCNPs                               | Ce6, Rose Bengal   | N/A                            | 808 nm       | Synergistic PDT                                                                         |      |
|                                     | Rose Bengal, zinc (II) phthalocyanine | Poly(allylamine)            | 980 nm       | Endosomes/lysosomes and mitochondria localization; synergetic PDT                       | [107]|
| Amphiphilic micelle                 | Ce6                 | DOX                            | 660 nm       | Chemo-PDT                                                                               |      |
| HSA-Ce6-catalase-PTX nanoparticles  | Ce6                 | PTX                            | 660 nm       | Chemo-PDT                                                                               | [113]|
| Reduced graphene oxide/mesoporous   | Ce6                 | N/A                            | 808 nm       | PDT-PTT                                                                                 | [110]|
| silica/hyaluronic acid nanocomposite| UCNPs               | Ce6                            | 980 nm       |                                                                                         |      |
| Polymer-coated UCNPs               | Ce6                 | Alpha-cyclodextrin; DOX         | 980 nm       | Chemo-PDT                                                                               | [115]|
| Lipid-calcium-phosphate nanoparticles| Photosan            | VEGF-A small interfering RNA   | 640 nm       |                                                                                         | [117]|
| PEGylated iron oxide nanoclusters  | Ce6                 | PEG                            | 661 nm 704 nm| Fluorescence/MRI dual-mode imaging + PDT                                                  | [32] |
| MnFe2O4-anchored mesoporous silica nanoparticles | Ce6              | N/A                            | 680 nm       | MRI + oxygen enriched PDT                                                                | [118]|
| Two-dimensional tellurium nanosheets | Tellurium           | Glutathione                    | 670 nm       | Multispectral optoacoustic tomography + PDT                                               | [119]|
| Au/Ag–MnO2 hollow nanospheres      | Ce6                 | PEG                            | 808 nm 1064 nm| Fluorescence/MRI/ photoacoustic imaging + oxygen enriched PDT + deep PTT                | [120]|

in the inflammatory sites or the tumour microenvironment can trigger the bioluminescence resonance energy transfer and the production of $^{1}O_2$ from the nanoparticle, enabling in vivo imaging and antitumor activity [105]. Jiang et al constructed an in-situ luminescing and $O_2$-supplying system for efficient PDT based on luminol-$H_2O_2$-Hemoglobin (Hb). Hb conjugated polymer nanoparticles simultaneously catalysed the chemiluminescence and internal activation of luminol/$H_2O_2$ and served as the carrier for delivering sufficient molecular oxygen, which led to more ROS generation and enhanced cytotoxicity in PDT under a hypoxia condition [106].

7. Multifunctional nano-PSs for combinational therapies and theragnostic PDT

Taking advantage of the unique physiochemical properties of nanomaterials, additional functionalities can be incorporated in the design of nano-PSs for either multidrug delivery involved in combination therapy or synergetic imaging for diagnostic analysis and imaging-guided therapy. Some representative multifunctional nano-PSs used in combinational or theragnostic PDT were summarized in table 3. With the ease of co-encapsulating of multiple agents, more than one PS can be loaded in the nanocarriers to achieve significantly improved synergetic anticancer effects. For example, Lee et al loaded two PSs, Ce6 and Rose Bengal, to UCNPs with a core@shell structure (NaYF4:Yb,Er,Nd@NaYF4:Yb,Nd) and found the dual PS system showed a synergetic ROS generation, which is significantly higher than that of a single PS system [107]. As shown in figure 10, Chang et al constructed the core/shell UCNPs-PS modified with poly(allylamine) for intracellular targeting and dual-loaded with two PSs, i.e. Rose Bengal and Zinc(II) phthalocyanine, to achieve better therapeutic PDT effects on A549 cells [108]. Besides the PS molecules, other anticancer therapeutics can also be co-delivered to the targeted tumour sites, and noted synergistic therapeutic outcomes have been achieved upon the combination with chemotherapy, PTT [109, 110], ionizing radiation [111], or gene therapy [112].

In the case of combining PDT with chemotherapy, PDT-induced ROS can suppress the active efflux translocator and consequently inhibit the efflux of chemotherapeutics. As such, PDT and chemotherapy drugs can mutually promote the therapeutic efficacy on a synergy basis. DOX [113, 121], paclitaxel [114], mitomycin [122], and cisplatin [123] have been often combined with PSs to develop the integrated
nanosystems. In one example, Tian et al designed α-CD modified red-emitting UCNPs to co-deliver both Ce6 and DOX for combined deep PDT/chemotherapy under 980-nm laser irradiation, where a much higher efficiency was found as compared to individual ones [115]. Liu et al recently reviewed the UC-based PDT where additive benefits and profound therapeutic effects were highlighted as a result of the integration of UCNPs with other traditional therapies [124].

The *in vivo* tumoricidal effect of PDT is not only capable of eliminating primary tumours but also has demonstrated its potency of sensitizing the immune system to destroy metastasis and prevent tumour relapse. We have recently reviewed the PDT facilitated-antitumor immunity based on various immunotherapeutic approaches in concert with PDT, among which nano-PSs became a powerful means for PDT-induced immunity via tuneable delivery of multiple immunostimulatory agents [125]. Xu et al designed a UCNP-based platform by co-loading Ce6 and imiquimod (R837), a Toll-like-receptor-7 agonist as an immune adjuvant, onto the polymer-coated UCNPs for NIR-assisted deep PDT of colorectal cancer [116]. In addition to photodynamic destruction of primary tumours upon 980-nm light irradiation, the nano-PSs were able to trigger the maturation of DCs and subsequent secretion of cytokines which significantly strengthened the antitumor immune responses.

The cytotoxic T-lymphocyte-associated protein 4 blockade could further inhibit the activities of T_reg cells and destroy distant tumours that is normally hard to reach with the light for PDT.

In addition, as part of the inflammatory responses, localized damage of tumour vasculature is another therapeutic effect of PDT. The extent of PDT-triggered vascular damage can be further exacerbated by synergistically combining with inhibitors against angiogenesis factors such as vascular endothelial growth factor (VEGF), tumour necrosis factor (TNF-α), and interleukin-1β. Lecaros et al reported their study of combining PDT with targeted VEGF-A gene therapy to achieve an enhanced therapeutic outcome for human head and neck squamous cell carcinoma (HNSCC) [117]. Lipid-calcium-phosphate nanoparticles were used to deliver VEGF-A small interfering RNA to significantly decrease the expression of VEGF-A, which is overexpressed under the hypoxic conditions during PDT. The combination of VEGF-A siRNA gene therapy and photosan-mediated PDT did result in a significant antiangiogenic effect by silencing the angiogenic markers and led to the tumour growth rate decrease of ~70 and ~120% in comparison to untreated group in subcutaneous human HNSCC xenograft models.

Aside from being as transporting vehicles of PSs or as energy transducers in photodynamic reaction, nanomaterials have also endowed additional capabilities in imaging for diagnoses. Owing to the intrinsic fluorescence of most PSs, the biodistribution of nano-PSs is traceable using the *in vivo* whole-body fluorescence imaging system [36]. Other nanomaterials such as magnetic nanoparticles and quantum dots by themselves are well-established nanoplatforms used for optical imaging and magnetic resonance imaging (MRI) as contrast agents, and have been continuously adopted for PS delivery in PDT with concurrent diagnosis abilities [126, 127]. Lamch et al scrutinized the recently engineered multifunctional colloidal nanoparticles for enhanced PDT and bioimaging, with an emphasis on the design principles and the comparison of bio-performance of various nano-PS platforms [35].

In one example, Li et al developed PEGylated iron oxide nanoclusters (IONCs) to load the PS molecule of Ce6 for PDT with demonstrated efficacy *in vitro* and *in vivo* [32]. Meanwhile, taking advantage of the strong
magnetic resonance signals attributed to IONCs and intra-tumoural fluorescence of Ce6, the IONCs-Ce6 could also be used for fluorescence-MRI dual-mode imaging of cancer while achieving the magnetic-guided PDT by an external magnetic field. Kim et al designed Ce6-loaded and manganese ferrite nanoparticle (MnFe₂O₄)-anchored mesoporous silica nanoparticles (MFMSNs) for enhancing the therapeutic efficiency of PDT by relieving the hypoxic conditions [118]. Besides continuous supply of oxygen through the catalytic Fenton reaction to improve the PDT effects, MnFe₂O₄ nanoparticles also served as the T2-contrast agent for in vivo MRI tracking. After intravenous injection, Ce6-loaded MFMSNs were selectively retained at the tumour sites owing to the EPR effect. Lin et al reported the synthesis of two-dimensional tellurium nanosheets, which could generate ROS and exhibit high imaging performance for multispectral optoacoustic tomography due to the strong NIR absorbance [119]. Clearly, this material can be further engineered as a nanoplatform for photoacoustic imaging-guided PDT. Wu et al fabricated Ce6-loaded Au/Ag-MnO₂ hollow nanospheres with multifunction of endogenous oxygen generation for enhanced PDT, remarkable photothermal conversion in the NIR window for deep PTT, and triple-modal (fluorescence/photoacoustic/magnetic resonance) imaging for diagnosis [120].

8. Future perspectives and concluding remarks

The emerging nano-PSs will not only address the current impediments in PDT by significantly improving the overall PS pharmacokinetics and guiding tumour-specific accumulation but also provide alternatives for deep PDT as energy donors under NIR to increase the treatment depth. However, with similar obstacles to other nanomedicine, nano-PSs also face great challenges in clinical translations. Prior to successful clinical utility, the in vivo performance of nano-PSs via different administration routes, including the blood retention, tissue penetration capability, and their possible interactions with serum proteins and immune system, must be thoroughly investigated. Despite the increasing efforts in unravelling the systemic response, biodistribution and pharmacokinetics of various particulates in nano scale, limited information has been gathered regarding the long-term effects of nanoparticles inside the human body.

Many of current researches on nano-PSs still primarily focus on the innovative design of nanostructures. During the fabrication process of multifunctional nano-PSs, nanomaterials normally need to undergo a complicated synthesis route that requires multiple reagents, followed by a series of surface modification, purification, chemical extraction, and centrifugation steps. This could be further complicated with the involvement of more than one PSs, other therapeutic agents, targeting ligands or functional motifs for combinational therapy, intracellular delivery, and/or theragnostic functions. The large variation in experimental setup and the lack of standardization of methodologies would bring in another dimension of challenges in reproducibility, scalability, and quality control, which hamper the translation of research findings to bedside.

Moreover, during a typical fabrication process of nano-NPs, covalent conjugation tends to lower the quantum yields of PSs, and the involvement of hydrophilic coatings may induce PS aggregation and diminish the ROS generation efficiency. In this regard, it is always noteworthy that rational functionalization of nanocarriers should not compromise the photophysical properties of PSs during the encapsulation of PSs in various nanostructures. It remains elusive to determine the optimal cocktails of material composition and ratios of each functional motifs across or/and within various modalities. Collectively, the delicate balance of multiple factors in the design of nano-PSs has thus been a major bottleneck, resulting in the current nano-PSs being stuck in the research phase.

Furthermore, more in-depth mechanistic understanding of the photophysical properties of nano-PSs upon different physicochemical stimulations becomes essential, accompanying with substantial improvement in analytical technologies for localized molecular imaging, and intracellular ¹⁸O₂ tracing without additional probes.

In addition, in order to bring nano-PSs closer to clinical PDT application, it is always essential to perform preclinical tests to confirm the biosafety and the in vivo therapeutic index, and to verify the cancer-targeting capability based on experimental models that can closely mimic human responses. Tumour xenograft models are generally considered as necessary approaches to study the systemic effects of nano-PSs; however, due to the inherent genetic and immunological differences and large individual variations, murine models can barely represent the performance of nano-PSs in the human physiological systems. Moreover, as the administration route is also closely related to the systemic outcomes, it will be necessary to monitor the dynamic interactions between tumour cells and nano-PSs in real time and to determine the fate of nanoparticles through extended observation of their biodistribution upon different administrations. In this regard, the recently established tumour-on-a-chip platforms could be beneficial for high throughput evaluation of PDT efficacy by providing physiologically relevant microenvironments with controlled mechanical and chemical cues [128, 129]. Despite the need of a consensus on in vivo performance of
nano-PPs, we still believe that engineered nano-PPs offer an innovative horizon toward future development of cancer therapeutics, and endow current PDT with new opportunities for broader clinical implications.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81827803 (Yang), 61875085 (Yang), 81727804 (Yang)).

ORCID iD

Hongjun Wang | https://orcid.org/0000-0003-3455-8523

References

[1] Castano A P, Demidova T N and Hamblin M R 2004 Mechanisms in photodynamic therapy: part one—photosensitizers, photochemistry and cellular localization Photodiagnosis Photodyn. Ther. 1 179–93
[2] Hu J, Lei Q and Zhang X 2020 Recent advances in photonomedicines for enhanced cancer photodynamic therapy Prog. Mater. Sci. 114 100685
[3] Baskaran R, Lee J and Yang S-G 2018 Clinical development of photodynamic agents and therapeutic applications Biomater. Res. 22 25
[4] Huang Z. 2005 A review of progress in clinical photodynamic therapy Technol. Cancer Res. Treat. 4 283
[5] Lan M, Zhao S, Liu W, Lee C, Zhang W and Wang P 2019 Photonsensitizers for photodynamic therapy Adv. Healthcare Mater. 8 1900152
[6] Abrahamse H and Hamblin M R 2016 New photosensitizers for photodynamic therapy Biochem. J. 473 347–64
[7] Park W, Cho S, Han J, Shin H, Na K, Lee B and Kim D H 2018 Advanced smart-photonsensitizers for more effective cancer treatment Biomater. Sci. 6 79–90
[8] Konan Y N, Gurny R and Allémann E 2002 State of the art in the delivery of photosensitizers for photodynamic therapy J. Photochem. Photobiol. B Biol. 66 89–106
[9] Yano S, Hirohara S, Obata M, Hagiya Y, Ogura S-I, Ikeda A, Kataoka H, Tanaka M and Joh T 2011 Current states and future views in photodynamic therapy J. Photochem. Photobiol. C Photochem. Rev. 12 46–67
[10] Yan K, Zhang Y, Mu C, Xu Q, Jang X, Wang D, Dang D, Meng L and Ma J 2020 Versatile nanoplatforms with enhanced photochemistry: designs and applications Theranostics 10 7287–318
[11] Tang R, Habimana-Griffith L M M, Lane D D, Egbulefu C and Achilefu S 2017 Nanophotosensitive drugs for light-based cancer therapy: what does the future hold? Nanomedicine 12 1191–5
[12] Lim C K, Heo J, Shin S, Jeong K, Seo Y H, Jang W D, Park C R, Park S Y, Kim S and Kwon I C 2013 Nanophotosensitizers toward advanced photodynamic therapy of cancer Cancer Lett. 334 176–87
[13] Tada D B and Baptista M S 2015 Photonsensitizing nanoparticles and the modulation of ROS generation Front. Chem. Sci. 3 1–14
[14] Chen J, Fan T, Xie Z, Zeng Q, Xue P, Zheng T, Chen Y, Luo X and Zhang H 2020 Biomaterials advances in nanomaterials for photodynamic therapy applications: status and challenges Biomaterials 237 119827
[15] Ma H, Peng Q, An Z, Huang W and Shuai Z 2018 Efficient and long-lived room-temperature organic phosphorescence: theoretical descriptors for molecular designs J. Am. Chem. Soc. 141 1010–5
[16] Obaid G, Breukhaar F M, Bulin A L, Huang H C, Kuriakose J, Liu J and Hasan T 2016 Photonomedicine: a convergence of photodynamic therapy and nanotechnology Nanoscale 8 12471–503
[17] Huang Y Y, Sharma S K, Dai T, Chung H, Yaroslavsky A, Garcia-Diaz M, Chang J, Chiang L Y and Hamblin M R 2012 Can nanotechnology potentiate photodynamic therapy? Nanotechnol. Rev. 11 111–46
[18] Moret F, Scheiglmann D and Reddi E 2013 Folate-targeted PEGylated liposomes improve the selectivity of PDT with meta-tetracyclohexylchlorin (m-THP) Photocem. Photobiol. Sci. 12 823–34
[19] Sadasivam M, Avci P, Gupta G K, Lakshmanan S, Chandran R, Huang Y J, Kumar R and Hamblin M R 2013 Self-assembled liposomal nanoparticles in photodynamic therapy Eur. J. Nanommed. 5 115–29
[20] Yan L, Miller J, Yuan M, Liu J F, Busch T M, Tsourkas A and Cheng Z 2017 Improved photodynamic therapy efficacy of protoporphyrin IX-loaded polymeric micelles using erlotinib pretreatment Biomacromolecules 18 1836–44
[21] Avci P, Sibel Erdem S and Hamblin M R 2014 Photodynamic therapy: one step ahead with self-assembled nanoparticles J. Biomed. Nanotechnol. 10 1937–52
[22] Klaerner B, Rozanek M and Bryszewsk M 2012 Dendrimers in photodynamic therapy Curr. Med. Chem. 19 4903–12
[23] Narsireddy A, Vijayashree K, Adimoolam M, Manorama S V and Rao N M 2015 Photosensitizer and peptide-conjugated PAMAM dendrimer for targeted in vivo photodynamic therapy Int. J. Nanomed. 10 6865–78
[24] Conte C, Maiolino S, Pellioli D S, Miro A, Urago F and Quaglia F 2016 Polymeric nanoparticles for cancer photodynamic therapy Topics in Current Chemistry vol 370 (Berlin: Springer) pp 61–112
[25] Lee Y E and Kopelman R 2011 Polymeric nanoparticles for photodynamic therapy Methods Mol Biol 726 151–78
[26] Hong S H and Choi Y 2018 Mesoporous silica-based nanoplatforms for the delivery of photodynamic therapy agents J. Pharm. Investig. 48 3–17
[27] Bayir S, Barras A, Boukherroub R, Szunerits S, Raehm L, Richter S and Durand J O 2018 Mesoporous silica nanoparticles in recent photodynamic therapy applications Photocem. Photobiol. Sci. 17 1651–74
[28] Yang Y, Hu Y, Du H, Ren L and Wang H 2018 Colloidal plasmonic gold nanoparticles and gold nanorings: shape-dependent generation of singlet oxygen and their performance in enhanced photodynamic cancer therapy Int. J. Nanomed. 13 2665–78
[29] Hu Y, Yang Y, Wang H and Du H 2015 Synergistic integration of layer-by-layer assembly of photosensitizer and gold nanorings for enhanced photodynamic therapy in the near infrared ACS Nano 9 8744–54
[30] Yang Y, Hu Y, Du H and Wang H 2014 Intracellular gold nanoparticle aggregation and their potential applications in photodynamic therapy Chem. Commun. 50 7287–90
Wang J, Sun J, Hu W, Wang Y, Chou T, Zhang B, Zhang Q, Ren L and Wang H 2020 A porous Au@Rh bimetallic core–shell nanostructure as an H2O2-driven oxygenator to alleviate tumor hypoxia for simultaneous bimodal imaging and enhanced photodynamic therapy Adv. Mater. 32 2001862

Li Z, Wang C, Cheng L, Gong H, Yin S, Gong Q, Li Y and Liu Z 2013 PEG-functionalized iron oxide nanoclusters loaded with chlorin et for targeted, NIR light induced, photodynamic therapy Biomaterials 34 9160–70

Xu W, Qian J, Hou G, Wang Y, Wang J, Sun T, Ji L, Luo A and Yao Y 2019 A dual-targeted hyaluronic acid-gold nanorod platform with triple-stimuli responsiveness for photodynamic/photothermal therapy of breast cancer Acta Biomater. 83 400–13

Zhang Y, Ma N, Luo C, Zhu J and Bao C 2020 Photostimulator-laden cell membrane biomimetic nanoparticles for enhanced tumor synergic photothermal therapy RSC Adv. 10 9378–86

Lamch L, Pucek A, Kulbacka I, Chudy M, Iastrăţeţeu E, Tokarska K, Bulkia M, Brzózka Z and Wilk K A 2018 Recent progress in the engineering of multifunctional colloidal nanoparticles for enhanced photodynamic therapy and bioimaging Adv. Colloid Interface Sci. 261 62–81

Asem H, El-Fattah A A, Nafee N, Zhao Y, Khalil M, Hassan M and Kandil S 2016 Development and biodistribution of a theranostic aluminum phthalocyanine photosensitizer Photodiagnosis Photody. Ther. 13 48–57

Han K, Ma Z and Han H 2017 Functional peptide-based nanoparticles for photodynamic therapy J. Mater. Chem. B 6 25–38

Li Z, Wang C, Deng H, Wu J, Huang H, Sun R, Zhang H, Xiong X and Feng M 2019 Robust photodynamic therapy using 5-ALA-incorporated nanocomplexes cures metastatic melanoma through priming of CD4+ CD8+ double positive T cells Adv. Sci. 6 1802057

Chen Q, Chen J, Yang Z, Zhang L, Dong Z and Liu Z 2018 NIR-II light activated photodynamic therapy with protein-capped gold nanoclusters Nano Res 11 5657–69

Panikar S S, Ramirez-Garcia G, Vallejo-Cardona A A, Banu N, Patrón-Soberano O A, Cialla-May D, Camacho-Villegas T A and De La Rosa E 2019 Novel anti-HER2 peptide-conjugated theranostic nanopiloposomes combining NaYF₄: yb,Er nanoparticles for NIR-activated bioimaging and chemo-photodynamic therapy against breast cancer Nanoscale 11 20598–613

Kato T et al 2018 Preclinical investigation of folate receptor-targeted nanoparticles for photodynamic therapy of malignant pleural mesothelioma Int. J. Oncol. 53 2034–46

Li D, Wang X Z, Yang L F, Li S C, Hu Q Y, Li X, Zheng B Y, Ke M R and Huang J D 2019 Size-tunable targeting-triggered nanophotosensitizers based on self-assembly of a phthalocyanine-biotin conjugate for photodynamic therapy ACS Appl. Mater. Interfaces 11 56435–43

Jo H and Ban C 2016 Aptamer-nanoparticle complexes as powerful diagnostic and therapeutic tools Exp. Mol. Med. 48 230

Hong E J, Choi D G and Shim M S 2016 Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials Acta Pharmac. Sin. B 6 297–307

Montaseri H, Kruger C A and Abrahamse H 2020 Review: organic nanoparticle based active targeting for photodynamic therapy treatment of breast cancer cells Oncotarget 11 2120–36

Wang C, Liu J, Cao H and Zhang W 2017 Intracellular GSH-activated galactoside photosensitizers for targeted photodynamic therapy and chemotherapy Biomater. Sci. 5 724–84

Sobolev A S, Jans D A and Rosenkranz A A 2000 Targeted intracellular delivery of photosensitizers Prog. Biophys. Mol. Biol. 73 51–90

Deng W et al 2020 Application of mitochondrially targeted nanoconstructs to neoadjuvant x-ray-induced photodynamic therapy for rectal cancer ACS Cent. Sci. 6 715–26

Zhou Z, Liu J, Huang J, Rees T W, Wang Y, Wang H, Li X, Chao H and Stang P J 2019 A self-assembled Ru–Pt metallacage as a lysosome-targeting photosensitizer for 2-photon photodynamic therapy Proc. Natl Acad. Sci. USA 116 20296–302

Cheng H, Zheng R R, Fan G L, Fan J H, Zhao L P, Jiang X Y, Yang B, Yu X Y, Li S Y and Zhang X Z 2019 Mitochondria and plasma membrane dual-targeted chimeric peptide for single-agent synergistic photodynamic therapy Biomaterials 188 1–11

Gomes-da-silva L C et al 2018 Photodynamic therapy for redaptin targets the endoplasmic reticulum and Golgi apparatus Embio J. 37 e93553

Pan L, Liu J and Shi J 2018 Cancer cell nucleus-targeting nanocomposites for advanced tumor therapeutics Chem. Soc. Rev. 47 6930–46

Yang Y, Ren L and Wang H 2017 Strategies in the design of gold nanoparticles for intracellular targeting: opportunities and challenges Ther. Deliv. 8 879–90

Wang S, Huang P and Chen X Y 2016 Hierarchical targeting strategy for enhanced tumor tissue accumulation/retention and cellular internalization Adv. Mater. 28 7340–64

Nag O K and Delechanty J B 2019 Active cellular and subcellular targeting of nanoparticles for drug delivery Pharmaceutica 11 543

Yu Z, Sun Q, Pan W, Li N and Tang B 2015 A near-infrared triggered nanophotosensitizer inducingdomino effect on mitochondrial reactive oxygen species burst for cancer therapy ACS Nano 9 11064–74

Yang L, Gao P, Huang Y, Lu X, Chang Q, Pan W, Li N and Tang B 2019 Boosting the photodynamic therapy efficiency with a mitochondria-targeted nanophotosensitizer Chinese Chem. Lett. 30 1293–6

Yang Y, Gao N, Hu Y, Jia C, Chou T, Du H and Wang H 2015 Gold nanoparticle-enhanced photodynamic therapy: effects of surface charge and mitochondrial targeting Therapeutic Delivery 6 307–21

Song Y, Shi Q, Zhu C, Luo Y, Lu Q, Li H, Ye R, Du D and Lin Y 2017 Mitochondrial-targeted multifunctional mesoporous Au@Pt nanoparticles for dual-mode photothermal and photodynamic therapy of cancers Nanoscale 9 15813–24

Pan L, Liu J and Shi J 2014 Intracellular photosensitizer delivery and photosensitization for enhanced photodynamic therapy with ultralow irradiance Adv. Funct. Mater. 24 7318–27

Hu W, Ma H, Hou B, Zhao H, Ji Y, Jiang R, Hu X, Lu X, Zhang L, Tang Y, Fan Q and Huang W 2016 Engineering lysosome-targeting BODIPY nanoparticles for photosensitizing imaging and photodynamic therapy under near-infrared light ACS Appl. Mater. Interfaces 8 12039–47

Xiong H J, Deng Q, An L, Guo M, Yang S P and Liu J G 2016 Tumor cell specific and lysosome-targeted delivery of nitric oxide for enhanced photodynamic therapy triggered by 808 nm near-infrared light Chem. Commun. 52 148–51

Zhou Z, Liu J, Huang J, Rees T W, Wang Y, Wang H and Li X 2019 A self-assembled Ru–Pt metallacage as a lysosome-targeting photosensitizer for 2-photon photodynamic therapy Proc. Natl Acad. Sci. U.S.A. 116 20296–302

Mahalingam S M, Ordzaj J D and Low P S 2018 Targeting of a photosensitizer to the mitochondrion enhances the potency of photodynamic therapy ACS Omega 3 6066–74

Battaglotti G, Cho Y Y, Lee J Y, Lee H S and Kang H C 2018 Mitochondrial-targeting anticancer agent conjugates and nanocarrier systems for cancer treatment Front. Pharmacol. 9 922
[66] Wang Z, Guo W, Kuang X, Hou S and Liu H 2017 Nanopreparations for mitochondria targeting drug delivery system: current strategies and future prospective Asian J. Pharm. Sci. 12 498–508
[67] Pathak R K, Kolishetti N and Dhar S 2015 Targeted nanoparticles in mitochondrial medicine Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 7 313–29
[68] Wang S, Hützmann G, Rudnitzki F, Diddens-Tschoeke H, Zhang Z and Rahamanzadeh R 2016 Indocyanine green as effective antibody conjugate for intracellular molecular targeted photodynamic therapy J. Biomed. Opt. 21 078001
[69] Falanga A, Lombardi L, Galdiero E, Del Genio V and Galdiero S 2020 The world of cell penetrating: the future of medical applications Future Med. Chem. 12 1431–46
[70] Xie J, Bi Y, Zhang H, Dong S, Teng L, Lee R J and Yang Z 2020 Cell-penetrating peptides in diagnosis and treatment of human diseases: from preclinical research to clinical application Front. Pharmacol. 11 697
[71] Mossalam M, Dixon A S and Lim C S 2010 Controlling subcellular delivery to optimize therapeutic effect Ther. Deliv. 1 169–93
[72] Wang F, Salviati A and Boya P 2018 Lysosome-dependent cell death and deregulated autophagy induced by amine-modiﬁed polystyrene nanoparticles Open Biol. 8 8170271
[73] Zhuang J, Yang H, Li Y, Wang B, Li N and Zhao N 2020 Efficient photosensitizers with aggregation-induced emission characteristics for lysosomal- and gram-positive bacteria-targeted photodynamic therapy Chem. Commun. 56 2630–3
[74] Huai Y, Hossen M N, Wilhelm S, Bhattacharyya R and Mukherjee P 2019 Nanoparticle interactions with the tumor microenvironment Biomom. Chem. 30 2247–63
[75] Du J, Lane I A and Nie S 2015 Stimuli-responsive nanoparticles for targeting the tumor microenvironment J. Control. Release 219 205–14
[76] Liu H, Jiang W, Wang Q, Xia J, Yu W, Wang Y and Wang Y 2020 Microenvironment-activated nanoparticles for oxygen self-supplemented photodynamic cancer therapy Biomater. Sci. 8 370–8
[77] Ping J, You F, Geng Z and Peng H 2019 Facile synthesis of ﬂuorinated nanophotosensitizers with self-supplied oxygen for efﬁcient photodynamic therapy Nanotechnology 30 345207
[78] Yang Z, Wang J, Ai S, Sun J, Mai X and Guan W 2019 Self-generating oxygen enhanced mitochondrial-targeted photodynamic therapy for tumor treatment with hypoxia scavenging Theranostics 9 6809–23
[79] Liu M, Wang J, Zheng X, Liu S and Xia Z 2018 Hypoxia-triggered nanoscale metal-organic frameworks for enhanced anticancer activity ACS Appl. Mater. Interfaces 10 24638–47
[80] Li X, Zheng B Y, Ke M R, Zhang Y, Huang J D and Yoon J 2017 A tumor-pH-responsive supramolecular photosensitizer for activatable photodynamic therapy with minimal in vivo skin phototoxicity Theranostics 7 2746–56
[81] Hu X, Gao Z, Tan H and Zhang L 2019 A pH-responsive multifunctional nanocarrier in the application of chemo–photodynamic therapy J. Nanomater. 2019 3898564
[82] Hu D, Pan M, Yu Y, Sun A, Shi K, Qu Y and Qian Z 2020 Application of nanotechnology for enhancing photodynamic therapy viaameliorating, neglecting, or exploiting tumor hypoxia View 1 et
[83] Wang Y, Xiong W, Niu M, Tian J and Xu X 2019 Hypoxia-active nanoparticles used in tumor theranostic Int. J. Nanomed. 14 3705–22
[84] Yang N, Xiao W, Song X, Wang W and Dong X 2020 Recent advances in tumor microenvironment hydrogen peroxide-responsive materials for cancer photodynamic therapy Nano-Micro Lett. 12 1–27
[85] Qian C, Yu J, Chen Y, Hu Q, Xiao X, Sun W, Wang C, Peng F, Shen Q D and Gu Z 2016 Light-activated hypoxia-responsive nanocarriers for enhanced anticancer therapy Adv. Mater. 28 3313–20
[86] Sivasubramanian M, Chuang Y C and Lo L W 2019 Evolution of nanoparticle-mediated photodynamic therapy: from superficial to deep-seated cancers Molecules 24 520
[87] Zhang J Y et al 2017 NaYbF₄ nanoparticles as near infrared light excited inorganic phosphorsiters for deep penetration in photodynamic therapy Nanoscale 9 2706–10
[88] Hamblin M R 2018 Upconversion in photodynamic therapy: plumbing the depths Dalt. Trans. 47 8571–80
[89] Gnanasammandhan M K, Idris N M, Bansal A, Huang K and Zhang Y 2016 Near-IR photoactivation using mesoporous silica-coated NaYF₄: yb,Er/Tm upconversion nanoparticles Nat. Protoc. 11 688–713
[90] Yuan Y, Min Y, Hu Q, Xing B and Liu B 2014 NIR photoregulated chemo- and photodynamic cancer therapy based on conjugated polyelectrolyte-drug conjugate encapsulated upconversion nanoparticles Nanoscale 6 11259–72
[91] Shen Y, Shihender A J, Ye D, Xu J J and Chen H Y 2016 Two-photon excitation nanoparticles for photodynamic therapy Chem. Soc. Rev. 45 6725–41
[92] Qiu H, Tan M, Oshukhansky T Y, Lovell I F and Chen G 2018 Recent Progress in upconversion photodynamic therapy Nanomaterials 8 1–18
[93] Ogawa K and Kobuke Y 2013 Two-photon photodynamic therapy by water-soluble self-assembled conjugated porphyrins Biomed. Res. Int. 2013 125658
[94] Sourdron A, Gary-Bobo M, Maynadier M, Garcia M, Majoral J P, Caminade A M, Mongin O and Blanchard-Desce M 2019 Dendrimeric nanoparticles for two-photon photodynamic therapy and imaging: synthesis, photophysical properties, innocuousness in daylight and cytotoxicity under two-photon irradiation in the NIR Chem.—A Eur. J. 36 5637–49
[95] Duan X, Jiang X, Bi Y, Li J, Liu P, Li S, Huang F, Ma Y, Xu Q H and Cao Y 2019 Red emitting conjugated polymer based nanophosensitizers for selectively targeted two-photon excitation imaging guided photodynamic therapy Nanoscale 11 185–92
[96] Karges J, Huang S, Maschietto F, Blacque O, Ciofini I, Chao H and Gasser G 2020 Rationally designed ruthenium complexes for 1- and 2-photon photodynamic therapy Nat. Commun. 11 1–13
[97] Zhou B, Zhao Q, Tang L and Yan D 2020 Tunable room temperature phosphorescence and energy transfer in ratiometric co-crystals ChemComm 56 7698
[98] Zhi J, Zhou Q, Shi H, An Z and Huang W 2020 Organic room temperature phosphorescence materials for biomedical applications Chem. An. Asian J. 15 947–57
[99] Gao R and Yan D 2017 Interface, layered host–guest long-afterglow ultrathin nanosheets: high-efficiency phosphorescence energy transfer at 2D conﬁned Chem. Sci. 8 590–9
[100] Gao R, Mei X, Yan D, Liang R and Wei M 2018 Nano-phosensitizer based on layered double hydroxide and isophthalic acid for singlet oxygenation and photodynamic therapy Nat. Commun. 9 2798
[101] Fritzen D L, Giordano L, Rodrigues L C V and Monteiro J H S K 2020 Opportunities for persistent luminescent nanoparticles in luminescence imaging of biological systems and photodynamic therapy Nanomaterials 10 2015
[102] Wang J, Li Y, Mao R, Wang Y, Yan X and Liu J 2017 Persistent luminescent nanoparticles as energy mediators for enhanced photodynamic therapy with fractionated irradiation J. Mater. Chem. B 5 5793–805

IOP Publishing J. Phys. Mater. 4 (2021) 014003 Y Yang and H Wang
