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Advanced Smart-photosensitizers for More Effective Cancer Treatment

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Abstract

Photodynamic therapy (PDT) based upon the use of light and photosensitizers (PSs) has been used as a novel treatment approach for a variety of tumors. It, however, has several major limitations in the clinics: poor water solubility, long-term phototoxicity, low tumor targeting efficacy, and limited light penetration. With advances in nanotechnology, materials science, and clinical interventional imaging procedures, various smart-PSs have been developed for improving their cancer-therapeutic efficacy while reducing the adverse effects. Here, we briefly review state-of-the-art smart-PSs and discuss the future directions of PDT technology.

Graphical abstract

Smart photosensitizers (PSs), combined with advanced Nano- and Biomaterial technology, have a great potential for effective cancer treatment.

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Keywords

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1. Introduction

Photodynamic therapy (PDT) utilizes light sensitive molecules to treat diseases. The light therapy has a history of more than 3,000 years.^{1, 2} The ancients used light to treat various diseases, such as psoriasis, rickets, edema, and skin cancer.³ Since the 1960s, PDT has been suggested as an alternative cancer therapy, and it began to be used clinically for the cancer treatment in the 1970s.^{4, 5} PDT treats cancers by irradiating a cancer site with a specific wavelength of light after administration of cancer-specific photosensitizers (PSs), which allows to reducing the systemic side effects that conventional non-specific anticancer drugs might cause otherwise. Currently, PDT has been shown to be effective against early cancers and recommended for inoperable cancer patients having many complications.^{6, 7} Clinical PDT has been frequently used for the treatment of breast cancer,⁸ gynecologic tumor,⁹ intraocular tumor,¹⁰ brain tumor,¹¹ head and neck cancer,¹² colorectal cancer,¹³ cutaneous malignancies,¹⁴ intraperitoneal cancer,¹⁵ cholangiocarcinoma¹⁶ and pancreatic cancer¹⁷. Two non-toxic components, PSs and light of a specific wavelength, are utilizing for killing specific cancer cells and tissues in an oxygen-dependent manner.¹⁸ PSs activated by the light of a specific wavelength transfers its energy to oxygen molecules, resulting in the production of cytotoxic reactive oxygen species (ROS) such as singlet oxygen ($^1\text{O}_2$) (Scheme 1a).^{19, 20} In general, PSs produce ROS through type 1 (electron transfer) and/or type 2 (energy transfer) reactions.²¹ Type I reactions produce radical and radical anion species (e.g., $\text{O}_2^{\cdot-}$ and $\text{HO}\cdot$), while type II reactions generate singlet oxygen ($^1\text{O}_2$).^{22, 23} The generated ROS kills cancer cells through oxidation of important biomolecules and organelles in the cancer cells.

To date, various types of PS have been developed for advancing PDT (Scheme 1b and Table 1).^{18, 24} The first-generation PSs includes porphyrin-based PSs such as Photofrin®.^{25, 26} Various forms of hematoporphyrin derivatives (HpD) have been commercialized for over 30 years and have been used for thousands upon thousands of patients in clinical trials.^{24, 27} However, the first-generation PSs were efficiently activated by only wavelengths shorter than 640 nm, so limited light tissue penetration is an issue.²⁴ Furthermore, the patients treated with first-generation PSs had to stay in a dark room for a long time because the administrated PS remains in tissue for 4–6 weeks.²⁴ The second-generation PSs were mostly developed in the late 1980s and consists of porphyrinoid compounds with porphyrin or porphyrin-based macrocyclic structures.²⁸ Typical second-generation PSs are chlorins, bacteriochlorins, phthalocyanines, pheophorbides bacteriopheophorbides, texaphyrins, and aluminum phthalocyanine tetrasulfonate (AlPcS4). The second-generation PSs can be excited at wavelengths longer than 640 nm, which allows deeper light penetration and enhances tumor specificity.^{29, 30} In addition, their short tissue accumulation times under 2 weeks allowed the early release of patients from the darkroom.^{31, 32} However, most of second-generation PSs are still hydrophobic in nature with limited solubility in aqueous

solution.³³ Thus, they are apt to aggregate under physiological conditions, significantly reducing the quantum yields of ROS production. Even in the case of water-soluble PSs, the accumulation selectivity at malignant sites is not high enough for clinical use.³³

In order for more diverse PSs to be used in clinical practice, several important points need to be satisfied³⁴; (1) The PS should dissolve well in water; (2) The PS should be specifically accumulated in cancer cells; (3) The PS should be excited at wavelengths longer than 650 nm, allowing deeper light penetration into the tissue; (4) The PS should be metabolized rapidly and discharged out of the body; and (5) The PS should be capable of accurately imaging disease sites through clinical imaging devices. In addition, a real-time system of dosimetry for the PSs should be developed to allow for optimal drug dose, light dose and drug light interval.

To meet these clinical demands, with advances in nanotechnology, materials science, and interventional imaging technology, various next-generation PSs are now being evaluated with the hope of their future use in patients who are suffering from cancer.^{35–39} Novel polymers or nanoparticle (NP) have been combined with PSs for improving the solubility and photoactivity in the physiological environment. Smart PSs designed to recognize the target tissue and regulate its photoactivity in the cancer micro-environment.^{40, 41} It is a representative form of the third generation PSs. The smart PSs utilize stimuli responsive materials and multifunctional NP for highly specific targeting and enhanced therapeutic response.^{42, 43} Recently, various clinical image-guided interventions have been introduced into the PDT. With the smart PSs and multimodal imaging tools, the cancer site can be accurately imaged and simultaneously treated.^{44–46} Indeed, those efforts in third-generation PSs with image guidance have significantly improved the therapeutic efficacy while decreasing side effects, compared to the conventional first and second generation PSs.⁴⁷ This mini-review will summarize the trends of recently developed smart PS, and their future clinical applications for tumor specific image-guided PDT will be discussed.

2. Stimuli-responsive PSs

As stated in the previous, nonspecific activation of PSs in normal tissues not only reduces the therapeutic effect of PS but also causes severe side effect such as skin burning,^{48, 49} which limits its clinical applications. The development of smart PSs exhibiting an activity in response to specific stimuli at disease sites is a promising strategy for highly tumor-specific PDT. Stimuli-sensitive PSs with highly water-solubility responding to tumor associated environments such as tumor specific enzymes or acidic pH have been developed for the targeted PDT.^{37, 41, 50–52} Tumor environment tend to become acidic due to abnormal fast metabolic processes of cancer cells such as Warburg effect,^{53, 54} and also increase the expression of specific enzymes such as matrix metalloproteinases (MMPs) and hyaluronidase for tumor cell metastasis.^{55, 56} Recently, Na and Hyeon developed a nanocomposite PS that can diagnose and treat drug-resistant heterogeneous tumors.³⁵ The hybrid nanocomposites combining self-assembling polymeric PSs and extremely small iron oxide NPs (ESIONs, ~ 3 nm) allowed to detect early tumors (approximately 3 mm in diameter) with fluorescence and magnetic resonance (MR) imaging, and successfully inhibited the growth of drug-resistant heterogeneous tumors. Na group has also developed a

tumor specific polymeric PS that reacts with hyaluronidase, which is highly expressed only in the tumor microenvironment.^{50, 57} The PS molecules attached to one HA polymer lose their photoactivity due to the fluorescence resonance energy transfer (FRET) effect, but they regain the photoactivity through enzymatic degradation in cancer cells.⁵⁷ As a result, the enzyme-responsive PSs have greater activity in cancer cells than in normal cells, thereby reducing the side effects and improving the therapeutic effects.⁵⁷

As another new approach, thermo-responsive smart PSs^{38, 58–60} have been developed using temperature sensitive polymers. Recently, Na, Lee, and Kim collaboration group reported a thermo-switchable polymeric PS (T-PPS) by conjugation of a conventional PS (i.e., Pheophorbide-a) and a thermosensitive polymer (i.e., hydroxypropyl cellulose). This temperature-sensitive PS exhibited highly selective photoactivity only above the lower critical solution temperature (LCST) of the polymer (Fig. 1),³⁸ at which the polymer's phase transition caused intermolecular structural change of the PS that eventually enabled the PS to be photo-sensitive. The temperature sensitive PS can reduce non-specific photochemical activation in normal cells by means of a heat-triggering system. Specifically, this PS can be used for a combination therapy of PDT and hyperthermia. It is expected that the T-PPS has the considerable potential not only as a new class of photomedicine in the clinics but also as a biosensor and drug delivery platform based on temperature responsiveness.

Although various stimuli-sensitive PSs, as described above, have been developed to date, their sensitivity to the various stimuli does not meet our expectation. For these stimuli-sensitive PSs to be used in clinical applications, more highly sensitive materials having improved disease specificity must be developed, and various target markers must be discovered through analysis of biological characteristics of diseases.

3. Nano-bio functionalized PSs for image-guided PDT

As NPs have unique characteristics such as optical/magnetic properties,^{61–63} shape, size, and chemical reactivity, they have gained much attention in the field of PDT for the functionalization of conventional PSs.^{64, 65, 66} The use of NPs in conjunction with PSs offers the following representative advantages: 1) effective PS delivery to the targeted cancer cells,⁶⁷ 2) easy phase transfer of hydrophobic PS into amphiphilic, supporting unhindered circulation in bloodstream,⁶⁸ 3) enhanced permeability and retention (EPR) effect for effective diffusion of PS into tumors,⁶⁹ 4) various surface chemistry for the functionalization with molecules enhancing the cellular uptake and targeting,^{70, 71} and 5) multiple functionality by combining the original properties of NP such as multi-modal imaging, with PS.^{72, 73}

As a new concept in cancer therapy, image-guided therapy is promising optimization of the therapeutic effect of PDT by combining existing imaging technology and nanotechnology.^{46, 74} In clinical trials, PSs such as 5-aminolevulinic acid (5-ALA) actually been used to perform the image-guided PDT with an optical image device.^{75, 76} Currently, various kinds of NP are being tried to utilize in the image-guided PDT by taking advantage of the unique characteristics of NPs. For example, NP enables the visualization of disease sites through optical/magnetic resonance imaging (MRI)/computed tomography (CT)

imaging, while PS on their surface generate ROS to treat the disease. The imaging properties of the NP not only provide tumor size and location information, but also help determining the optimal dose of a PDT. The monitoring of the therapeutic response of PDT can also help in deciding the future treatment options. A variety of inorganic and organic nanostructured PS, such as gold NP,^{77, 78} magnetic NP,^{35, 79, 80} carbon-based materials,⁸¹ mesoporous silica NP,^{82, 83} polymeric micelles,^{59, 84} and upconversion NP (UCNP),^{85, 86} have been actively developed by many researchers including our group for image-guided therapies.^{87–92} The imageable PSs can be visualized in real time through imaging devices to perform PDT, making sophisticated clinical procedures possible and convenient.

Regarding the recent progress in nanostructured PSs with various NPs, UCNP has been highlighted as it not only solves the problem of low tissue penetration of light, which is the biggest limitation of conventional PSs, but also enables bio-imaging.^{86, 93, 94} Hyeon group first reported the systemic administration of UCNP-based PSs followed by *in vivo* luminescence and MR imaging with the therapeutic effect of PSs upon indirect excitation with low energy near infrared (NIR) light (Fig. 2).⁸⁵ The NIR-to-visible upconversion of NaYF₄:Yb,Er/NaGdF₄ core-shell UCNP effectively induced PSs activation for PDT via energy transfer and the accumulation of UCNP-based PSs was clearly visualized in the tumors by its upconversion luminescence and T1 contrast property. More recently, Zhang group employed UCNPs as light transducers to convert deeply penetrating NIR light to UV-visible wavelengths matching that of the absorption spectrum of photosensitive therapeutics for photodynamic cancer therapy⁶⁵ and photo-activated control of gene expression⁹⁵.

Although the NP-functionalized PSs have shown many potential applications in PDT, it has several limitations to its commercialization and clinical utility. Difficulties in the quality control of NP is one of the hurdles because subtle changes in the composition of NP or multistep reaction and conjugation of PS can affect the size, morphology, and surface property of NP, and loading of PS. The lack of standardized evaluation procedures for nanomaterial-based agents is another limitation that impedes the development of clinically applicable NP-functionalized PSs. In addition, mechanistic studies of the bio-distribution and metabolism of NP-functionalized PS *in vivo* are still lacking, which limits our ability in predicting *in vivo* long-term toxicity of NP-functionalized PS and in determining dosage for clinical practice. If the *in vivo* toxicity and metabolic processes of NP and NP-functionalized PSs are obtained in the near future, the multifunctional NP-functionalized PSs could be used to treat a wide range of cancerous diseases in the clinics. Scientists and clinicians in this field should work in optimizing the NP-functionalized PSs while performing pharmacological analysis using appropriate animal models.

4. Multi-therapeutic PSs for Combinational Treatment of Cancer

Although PDT with smart PSs is beneficial for the cancer treatment, it is difficult to completely treat tumors with mono PDT. Combination PDT with chemotherapy,^{96,97} photothermal therapy (PTT),^{98–100} or cancer immunotherapy^{101, 102} has shown an improved therapeutic effect compared to the conventional PDT alone. The improved synergistic therapeutic effects are attributed to mutual complementation of the disadvantages while sharing the advantages of each treatment.

PDT has been tried to be combined with conventional chemotherapy using anticancer drugs.¹⁰³ The primary goal of combination PDT with chemotherapy is to treat multi-drug resistant (MDR) cancer, which is difficult to treat with chemotherapeutic drugs alone.¹⁰⁴ Na group reported that the combination of PDT and chemotherapy exhibited effective therapeutic effects for the treatment of MDR cancer by exploiting the synergistic effects.¹⁰⁵ Cancer cells are often resistant to anticancer drugs by effluxing anti-cancer drugs through the expression of P-Glycoprotein (P-gp). The P-gp expressed in the drug-resistant cancer cells can be inactivated by PDT. In detail, the ROS generated from the polymeric PSs induces the peroxidation of the cellular membranes of the cancer cells, thereby inhibiting the activity of P-gp. This series of processes ultimately improves the anti-cancer effects of the combination PDT with chemotherapy in the MDR cells. However, there is room for improvement for the combination PDT with anti-cancer drugs in controlling the drug release rates and low drug encapsulation efficiency, which may limit their therapeutic effect.¹⁰⁶

The combination therapy with PTT has also been frequently reported. NIR PTT, a minimally invasive cancer treatment converting photon energy into heat, using NIR wavelength (700–850 nm) absorption of NP has shown promising anticancer effect with no significant heating of normal tissues.^{98, 99} A recent study demonstrated a new type of combination PDT with PTT using organic NP consisting of a polydopamine NP (PD-NP) core and a PS-conjugated hyaluronic acid (PS-HA) shell (Fig. 3).¹⁰⁷ The PD-NP acts as both a quencher for PS and PTT agent. The PS-HA consists of a PS and cancer targeting hyaluronic acid (HA) that can not only cause PDT effects but also target cancer cells. In response to cancer-specific intracellular enzymes (e.g., hyaluronidase), the PS-HA-coated PD-NP exhibited an excellent singlet oxygen generation capacity for PDT. Furthermore, an efficient photothermal conversion capacity for PTT was also shown in the PS-hyaluronic acid conjugates shielded polydopamine nanoparticle (PHPD-NP). These properties provide superior therapeutic efficacy against cancer cells. In a mouse tumor model, the photo-mediated therapeutic effects of the PHPD-NP were much higher in cancer microenvironments compared to that in the normal tissue. As a result, the PHPD-NP showed a significant antitumor activity in the *in vivo* mouse tumor model. The superior therapeutic effect of the combination of PDT and PTT was consistent with recently published results by the Lin and Cai groups.¹⁰⁰

Combination therapies with PDT and chemotherapy or NIR-PTT could improve the therapeutic benefits in cancer treatment, through overcoming the limitations of traditional chemotherapy or PDT, such as the drug resistance and the limited light tissue penetration. In the future, it is expected that multiple combination methods integrating more than two treatment methods will be developed to overcome the disadvantages of each treatment and superior therapeutic effects. Most recently, tri-modal therapy combining PDT, PTT, and chemotherapy has been developed along with multiple image guidance, and this technology has been reported to have therapeutic effects beyond that of conventional PDT.^{108–110}

5. Nano-scintillators combined PSs for X-ray PDT

Porphyrin, a typical PS used for PDT, exhibits a strong absorbance at 400 nm (Soret band) and a weak absorbance at 600–800 nm (Q-band).¹¹¹ Therefore, the ROS production in

response to the Soret band is much higher than that by the Q-band.⁹⁸ However, because the ultraviolet (UV) wavelength has the disadvantage of a very low tissue transmittance, a NIR wavelength with relatively high tissue transmittance has been mainly used for PDT. Although greater than UV, the NIR's skin permeability is still not satisfactory. It can only penetrate 5–6 mm, which makes it difficult to transmit light to deeply located cancers in clinical condition.^{98, 112}

As an alternative to those low transmittance light sources for PDT, X-rays has recently raised attention.^{98, 113} Because conventional PSs cannot directly absorb X-rays, a scintillator that can convert X-rays to an appropriate wavelength becomes essential. Scintillating NPs can convert X-ray energy to light energy of UV wavelength, which activates the surrounding PSs through fluorescence resonance energy transfer (FRET).⁹⁸ In this regard, the X-ray PDT can treat deeply seated tumor tissues.⁹⁸ Furthermore, X-rays can be used as a source for radiation therapy that demonstrates a synergetic therapeutic effects of X-ray PDT.¹¹²

The scintillators used in the X-ray PDT require some appropriate physical and biological properties for effective PDT. Effective scintillators should have high radiation sensitivity, high scintillation effect, efficient energy transfer to the PS, and excellent biocompatibility.¹¹⁴ To meet these requirements, several types of rare earth based scintillating NP (BaFBr: Eu²⁺, BaFBr: Mn²⁺, LaF₃: Ce³⁺, and LaF₃: Tb³⁺) have been developed and used for X-ray PDT.⁹⁸

In particular, terbium oxide (Tb₂O₃) NP is well known as an effective scintillator.¹¹⁴ It becomes biocompatible when coated with silica leading to core-shell nano-scintillators (Tb₂O₃@SiO₂). A bio-inert silica layer is used to reduce the toxicity of NPs by preventing the release of rare-earth metal ions. Tb³⁺ ions exhibit fluorescence, which overlaps with the absorption wavelength of porphyrin and is therefore suitable for performing X-ray PDT. Bulin and co-workers recently reported the effectiveness of Tb₂O₃@SiO₂ NP with PS in X-ray PDT for the treatment of cancer (Fig. 4).¹¹⁴ The Tb₂O₃@SiO₂ NP could activate the PS molecules through X-ray energy conversion and eventually kill cancer cells. This representative study demonstrated the strong potential of the X-ray PDT using scintillating NPs.¹¹⁴

There are challenges in using the scintillating NPs for X-ray PDT. Precise X-ray irradiation at the site of a local cancer is difficult. Thus, if the scintillating NPs and porphyrins are not co-localized to the cancer site, the diffuse X-ray radiation would cause adverse effects on normal tissues. Therefore, it is crucial to develop a nano-scintillator capable of accurately targeting cancer. It is also important to maintain the stability of the scintillating NPs *in vivo* for the course of treatments. The NPs injected into body must be rapidly degraded and excreted. Combining X-ray PDT with multimodal image-guidance^{79, 89, 91} allow accurate x-ray irradiation to target cancer tissues, which would help reduce the side effects in normal tissue.

6. Immune-modulatory PSs for photodynamic immunotherapy

Cancer immunotherapy consists of harnessing our innate immune system to treat cancer.^{87, 115} Due to recent promising results in survival rate and recurrence rate,^{115, 116}

immunotherapy has been regarded as one of the most promising cancer therapies and various studies are on-going. It has been thought that PDT may enhance immune response and surveillance.^{117, 118} Recent studies have reported that PDT can activate the anti-cancer immune cells and effectively inhibit tumor growth with preventing the metastasis of cancer cells and the recurrence of cancer.^{119, 118} These motivating results has attracted many clinicians and researchers for photodynamic immunotherapy.^{101, 118}

PDT kills cancer cells by apoptosis and necrosis, and stimulates the host immune system.¹¹⁸ It triggers acute inflammation and leukocyte infiltration to the tumors, which increases the presentation of tumor-derived antigens to T cells.^{101, 118} Immune checkpoint blockade therapy, which targets regulatory pathways in T cells to enhance anti-tumor immune response, has recently emerged as a new strategy for cancer immunotherapy.¹²⁰

Transmembrane protein PD-L1 expressed on tumor cells points to the PD-1/PD-L1 pathway as a valuable target for the checkpoint blockade immunotherapy.^{121, 122} Lin's group reported a new approach for photodynamic cancer immunotherapy using immunogenic NP to augment the antitumor efficacy of PD-L1 antibody-mediated cancer immunotherapy (Fig. 5).¹²³ Zn-pyrophosphate NP composed of the PS pyrolipid, a lipid conjugate of pyropheophorbide-a, (ZnP@pyro) effectively killed cancer cells upon light irradiation directly by inducing apoptosis and/or necrosis and indirectly by disrupting the tumor vasculature and increasing tumor immunogenicity. More importantly, the ZnP@pyro-mediated PDT was reported to induce an immunogenic environment in tumors and sensitize tumors to PD-L1 checkpoint blockade therapy. As a result, the ZnP@pyro PDT combined with anti-PD-L1 not only eradicated 4T1 breast primary tumors but also prevented lung metastasis and inhibited pre-existing metastatic tumors by generating systemic antitumor immunity. These results indicate that NP-mediated PDT can potentiate the systemic efficacy of checkpoint blockade immunotherapies by activating the innate and adaptive immune systems in the tumor microenvironment. Interestingly, this PDT-based immunotherapy could simultaneously treat distant tumors in bilateral syngeneic mouse tumor models by inducing an abscopal effect. The abscopal effect usually described with ionizing radiation refers to regression of tumor outside of the irradiated volume.¹²⁴ Although the mechanism is unknown, it is thought to be immune modulated.^{101, 124}

Most recently, Liu and Peng's groups have proposed using a multi-functional NP composed of UCNPs, PS, and imiquimod (R837), a Toll-like-receptor-7 agonist simultaneously to overcome the disadvantages of conventional PDT such as limited penetration depth of light and low anticancer immune response.¹²⁵ The multifunctional nanoparticles induced an effective PDT effect with high tissue permeability in NIR wavelength laser due to the UCNP, and serve as an adjuvant, leading to a robust immune response induced by the tumor-associated antigen formed by the PDT treatment. More significantly, when combined with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoint blockade, it was shown to be more efficient in the antitumor immunities and inhibited the growth of distant tumors left behind after PDT treatment.

Although the immunotherapy combined with PDT is currently in its early stages, it is expected to have great potential in the future. In particular, introduction of the aforementioned functional smart PSs into photodynamic immunotherapy could effectively

treat various types of cancer as well as prevent cancerous diseases. However, detailed studies are needed to understand the biological role of PDT to improve the immune responses. In addition, the development of smart PSs with physiochemical properties suitable for immunotherapy will enable more effective combination cancer immunotherapy. The physicochemical properties can be the hydrophilicity/hydrophobicity, particle size, and surface charge of the smart PS. These properties can affect the interaction with tumor-associated antigens or immune cells.^{126, 127}

7. Conclusions and perspectives

PDT has been clinically used to treat a variety of cancers such as skin, esophageal cancer, lung, head and neck, liver, prostate cancer, and bladder cancer. However, the classical first and second-generation PSs have several limitations in clinical application, such as poor water solubility, low cancer targeting efficacy, long-term phototoxicity, and limited light penetration of tissue. To overcome the shortcomings of conventional PSs, new types of smart PSs have been of great interest in PDT cancer therapeutics with the development of nanotechnology or materials science. Smart PSs with highly water-solubility responding to various stimuli such as temperature, pH, and enzymes have been designed to more accurately target disease for improving the therapeutic efficacy in PDT. Nano-based PSs have also been studied to impart unique properties such as multi-modal medical imaging and therapeutic functions of NPs to the conventional PS. The smart PSs, multifunctional NPs combined with stimuli responsive PSs, have great potential for various combinational therapies overcoming the drug resistance of cancer cells and enhancing therapeutic efficacy. Among promising new combinational PDT therapies, X-ray PDT technology attracted one of great attention to mitigate the issue of limited light penetration in treating cancers located in deep tissues. Most recently, photodynamic immune therapy combined with the smart PSs and immune checkpoint blockade has also emerged as a new robust approach for treating cancers. This next-generation PS technology and its multidisciplinary convergence technology not only overcomes the shortcomings of the conventional PSs but also evolves into a new concept of PDT technology.

Thanks to those advanced in the technology of third-generation PSs, first NP-based PS, Visudyne® (Verteporfin), was recently approved by the Food and Drug Administration (FDA) in 2000 for the treatment of age-related macular degeneration.¹²⁸ In addition, two liposomal formulations of *m*-THPC, Foslip® and Fospeg®, were developed and are being evaluated.⁴⁷ However, the third-generation PSs still need a lot of improvement for clinical use in a wide range of cancer diseases. The improvement can be made in progress of physicochemical properties of the PSs or clinical surgical procedure for accurate light source delivery. Currently, PSs suitable for NIR wavelengths using advanced nanotechnology are being developed. Based on state-of the art interventional image-guidance, new clinical techniques are also being tried to accurately deliver the light source to cancer in deep tissue using an optical fiber or an endoscope. Lastly, in-depth studies of the biological mechanisms of third generation PSs with various chemical structures will provide valuable information on the biological interactions between organisms and PSs to improve their therapeutic efficacy. Those advanced techniques with better understanding in materials and clinical field

will permit real-time monitoring and treatment of tumors allowing optimized and personalized PDT therapies for each patient.

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Fig. 1. Temperature-responsive polymeric PS (T-PPS)

(a–b) (a) Chemical structure of the T-PPS and (b) their bioapplications. (c–d) Temperature-dependent change in (c) transmittance of T-PPS and native HPC (inset: photograph of T-PPS aqueous solution (10 mg/mL in water) at (1) $T < \text{lower critical solution temperature (LCST)}$ and (2) $T > LCST$), and (d) singlet oxygen generation of T-PPS in aqueous solution ($n = 3$, $*p < 0.001$). (e–f) *In vitro* photocytotoxicity of T-PPS at various temperatures on PANC-2 cells. (e) Cell counting based upon kit-8 (CCK-8) assay and (f) Live/dead assay for cell viability of PANC-2 cells incubated with T-PPS (concentration of PPb-a, 1 $\mu\text{g/mL}$) under laser irradiation (3.0 J/cm^2) at 37 °C and 45 °C ($n = 4$, $*p < 0.002$). Reproduced with permission from ref. 38. Copyright 2016 American Chemical Society.³⁸

Fig. 2. Upconverting nanoparticle (UCNP)-based smart photosensitizer (PS)

(a) Schematic illustration of luminescence and magnetic resonance (MR) imaging with photodynamic therapy (PDT) using UCNPs-based PS. (b) Transmission electron microscopy (TEM) image of NaYF₄:Yb,Er/NaGdF₄ core-shell UCNPs. (c) Bright field and upconversion luminescence images of a nude mouse bearing tumor after intravenous injection of UCNPs-based PS. (d) T1-weighted color maps of a tumor-bearing nude mouse before and 1.5 h after intravenous injection of UCNPs-based PS. Arrows indicate tumor sites. (e) Growth of tumors after treatments (n=3 for each group). Reproduced with permission from ref. 83. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.⁸⁵

Fig. 3. Smart photosensitizer (PS) for combination photodynamic therapy (PDT) and photothermal therapy (PTT)

(a) Chemical structure of polydopamine nanoparticle (PD-NP) and PS-conjugated hyaluronic acid (PS-HA) conjugates. (b) Schematic illustration of synergistic cancer therapy effect of PDT and PTT using PS-hyaluronic acid conjugates shielded polydopamine nanoparticle (PHPD-NP). (c) Scanning electron microscopy (SEM) image of PHPD-NP (scale bar: 100 nm). (d) Live/Dead assay of MDA-MB-231 cells treated with PHPD-NP with or without laser irradiation at 3.0 J/cm² power. (e) Tumor growth inhibition after intratumoral injection of phosphate-buffered saline (PBS), PD-NP, PS-HAs, or PHPD-NPs with laser irradiation (n = 4). Reproduced with permission from ref. 105. Copyright 2016 American Chemical Society.¹⁰⁷

Fig. 4. Smart PS for X-ray photodynamic therapy (PDT)

(a) Schematic illustration of the working mechanism of X-PDT. Under X-ray irradiation, nanoscintillator (Tb_2O_3) transfer energy toward the photosensitizer (PS, Porphyrin), leading to singlet oxygen generation. (b) Fluorescence spectra measurement performed with 300 nm excitation. The emission spectrum of porphyrin was almost zero, while the spectrum of the porphyrin grafted $Tb_2O_3@SiO_3$ nanoparticle (NP) presents both the emission peaks at 650 and 725 nm. Reproduced with permission from ref. 112. Copyright 2013 American Chemical Society.¹¹⁴

Fig. 5. Immunogenic nanoparticle (NP) for photodynamic cancer therapy

(a) Scheme illustration of the Zn-pyrophosphate (ZnP) core and the photosensitizer (PS) pyro-PS (a lipid conjugate of pyropheophorbide-a) shell of the immunogenic NP (ZnP@pyro). (b) Transmission electron microscopy (TEM) image showing the spherical and nearly monodispersed morphology of ZnP@pyro (scale bar = 200 nm). (c) Photographs of excised primary 4T1 tumors at the end point (23 days after tumor implantation). From top to bottom: phosphate-buffered saline (PBS), α -PD-L1, ZnP@pyro (+), and ZnP@pyro (+) + α -PD-L1. The tumors indicated with dot-lined rectangle disappeared in the ZnP@pyro (+) + α -PD-L1 group. This result suggests that the ZnP@pyro PDT combined with PD-L1 blockade eradicates primary 4T1 tumors and prevents lung metastasis. (d–e) (d) Distant and (e) primary tumor growth curves of 4T1 models. The arrows represent the time of NP administration (black) and irradiation (red). (f) Weight of 4T1 tumors at the end point (28 days after tumor implantation) of the experiment. “(+)” in the figure legends refers to treatment with irradiation. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. The combination of ZnP@pyro with irradiation and PD-L1 blockade induced complete eradication of the irradiated primary tumors (synergistic effect) and effective control of the nonirradiated distant tumors (abscopal effect), eliciting a 92% reduction in tumor size compared to the PBS control group. These results indicate that tumors can be sensitized to PD-L1 blockade immunotherapy by ZnP@pyro PDT-mediated tumor-specific immune responses. Reproduced with permission from ref. 121. Copyright 2016 American Chemical Society.¹²³

Scheme 1. Schematic diagram of the principle of photodynamic therapy (PDT) and the classification of photosensitizers (PSs) developed to date

(a) The mechanism of action of PDT is illustrated by the Jablonski diagram.¹⁹ When light (photon) is shone on PS, the PS can be excited to the first excited singlet state that can relax to the more long-lived triplet state. The triplet PS can interact with oxygen molecules to produce reactive oxygen species (ROS) through the type 1 and type 2 mechanisms. (b) Classification of the generations of PSs developed so far. Currently developed PSs can be divided into first generation and second-generation based upon their physico-chemical property. The third-generation of smart PSs functionalized with polymers or nanoparticle is currently under development.

Table 1

Clinically available photosensitizers (PSs) and their potential applications.
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Platform	Trade name	Substance	Manufacturer	Potential applications
Porphyrin	Photofrin®	HpD	Axcan pharma Inc.	Cervical, endobronchial, oesophageal, bladder, and gastric cancers, and brain tumors
porphyrin	Levulan®	5-ALA	DUSA Pharmaceuticals, Inc.	Basal-cell carcinoma, head and neck, and bladder tumors
porphyrin	Metvix®	5-ALA-methylesther	PhotoCure ASA	Basal-cell carcinoma
porphyrin	Hexvix®	5-ALA hexylesther	PhotoCure ASA	Diagnosis of bladder tumors
porphyrin	Visudyne®	Verteporfin	Novartis Pharmaceuticals	Basal-cell carcinoma
Chlorine	LS11, Photolon®, Litx™, Apoptosin™, Laserphyrin	Talaporfin	Light sciences	Solid tumors from diverse origins
Chlorine	Photochlor	HPPH	RPCI	Basal-cell carcinoma
Phthalocianines	Pc-4	Phthalocianine	CWRU	Cutaneous/subcutaneous lesions from diverse solid tumor origins