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REVIEW

# Photodynamic therapy with smart nanomedicine

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**Abstract** For several decades, clinical demands for utilization of photodynamic therapy (PDT) have been increasing. Notably, PDT was mainly applied for cancer therapy, and most photosensitizers (PSs) were developed to treat cancer. The advantages of PDT, such as minimal invasiveness and local treatment by topical light irradiation, have made it possible to widen the range of target diseases. Thus, PDT has been clinically used for treatment of various diseases (e.g., cancer, acne, and age-related macular degeneration). However, PS, which is the main component of PDT, exhibits several shortcomings such as low solubility, low bioavailability, and lack of lesion selectivity for use as a therapeutic agent. Therefore, many research projects have been performed to develop smart PS. To increase therapeutic efficacy and to decrease adverse effects in normal tissue at the same time, PS incorporation within nanoscaled delivery systems is evolving. This review provides a comprehensive explanation of PDT in smart nanomedicine, which is academically and clinically utilized in the treatment of various diseases.

**Keywords** Photodynamic therapy · Photosensitizer · Drug delivery · Nanotechnology · Nanomedicine

## Introduction

In 1900, the fact that light of specific wavelengths can be fatal to protozoa such as infusoria was discovered (Raab 1900). Many researchers tried to apply light for the treatment of smallpox, tuberculosis, cancer, and other diseases (Daniell and Hill 1991; Finsen 1895). In the 1960s, as shown in Fig. 1, modern photodynamic therapy (PDT) was initiated with the discovery of cancer diagnostic and therapeutic effects by injection of a hematoporphyrin derivative (Lipson and Baldes 1960; Lipson et al. 1961). After the first clinical approval of porfimer sodium (Photofrin®) in 1993 in Canada and the first US Food and Drug Administration (FDA) approval in 1995, PDT has become the most site-specific remedy applicable for cancers and has been clinically approved for the treatment of various cancers: esophageal cancer, lung cancer, endobronchial cancer, head and neck cancer, gastric cancer, biliary tract cancer, and papillary bladder cancer (Li et al. 2017). Another phototherapeutic agent, aminolevulinic acid (Levulan®), was clinically approved in 1999 for therapy of actinic keratosis, and temoporfin (Foscan®) based on chlorin was approved in 2001 for palliative treatment of head and neck cancer (Hwang et al. 2018). In addition, atherosclerotic plaques, rheumatoid arthritis, prophylaxis of arterial restenosis, and age-related macular degeneration (AMD) have been treated with PDT (Li et al. 2018c). In 2000, the FDA approved PDT as a remedy for AMD, which is the main cause of blindness in the elderly, due to impressive therapeutic effects of PDT in choroidal neovascularization (CNV).

PDT, a light-responsive therapeutic method, offers a number of advantages including minimal invasiveness, reduced long-term mortality, and tissue selectivity by topical irradiation (Kim et al. 2018a). This topical light-induced remedy provides better spatial selectivity than conventional

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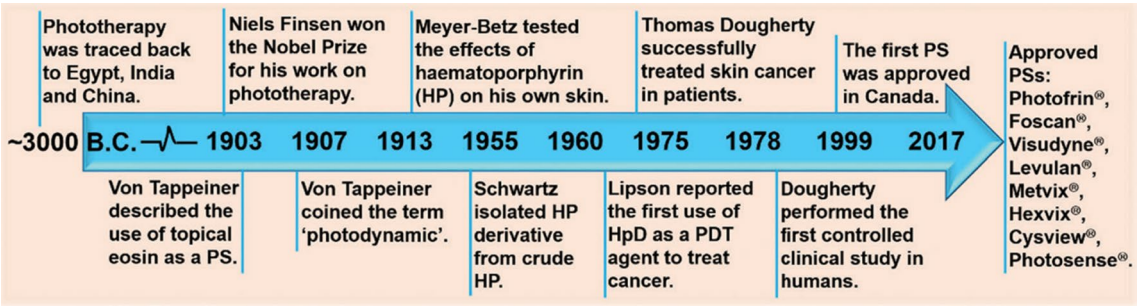


**Fig. 1** Timeline of PDT development. (Permission from Royal Society of Chemistry)

chemotherapy and radiotherapy. Phototherapy consists of two major stages. The first step is phototherapeutic agent delivery to the lesion, and the next step is light irradiation of the lesion for activation of the phototherapeutic agent, the photosensitizer (PS) (Abbas et al. 2017). For therapeutic activation in PDT, the light of wavelengths in the range of 600 to 800 nm is useful to avoid interference by endogenous chromophores including nucleic acids, amino acids, and melanin in the body and to generate cytotoxic species (Celli et al. 2010). The excitation of PSs results in not only a cytotoxic effect which is useful for eradication of abnormal cells but also emission of near-infrared (NIR) fluorescence by relaxation of the excited state back to the ground state (ho Hong and Choi 2018) (Fig. 2). The emitted fluorescence can be utilized for diagnosis of disease and identification of the ideal therapeutic window (Zhu et al. 2017). At the same time, PDT causes selective damage to the lesion site, occlusion of surrounding vasculature, and host immune induction with minimal off-target side effects (Hwang et al. 2018; Jeon and Ko 2019). For these reasons, PDT has performed as a clinically promising method for the treatment of cancer (Li et al. 2018a). In addition, bacterial and fungal infections due to microorganisms have also been widely treated using PDT for more than three decades (Li et al. 2018b).

PS, one of the essential factors for PDT, is a light-sensitive material and does not present toxicity; under a specific wavelength, it can be used as a therapeutic agent (Abbas et al. 2017). Activated PS transfers energy to oxygen molecules and consequently produces reactive oxygen species (ROS) (Kim et al. 2018a). ROS oxidize important

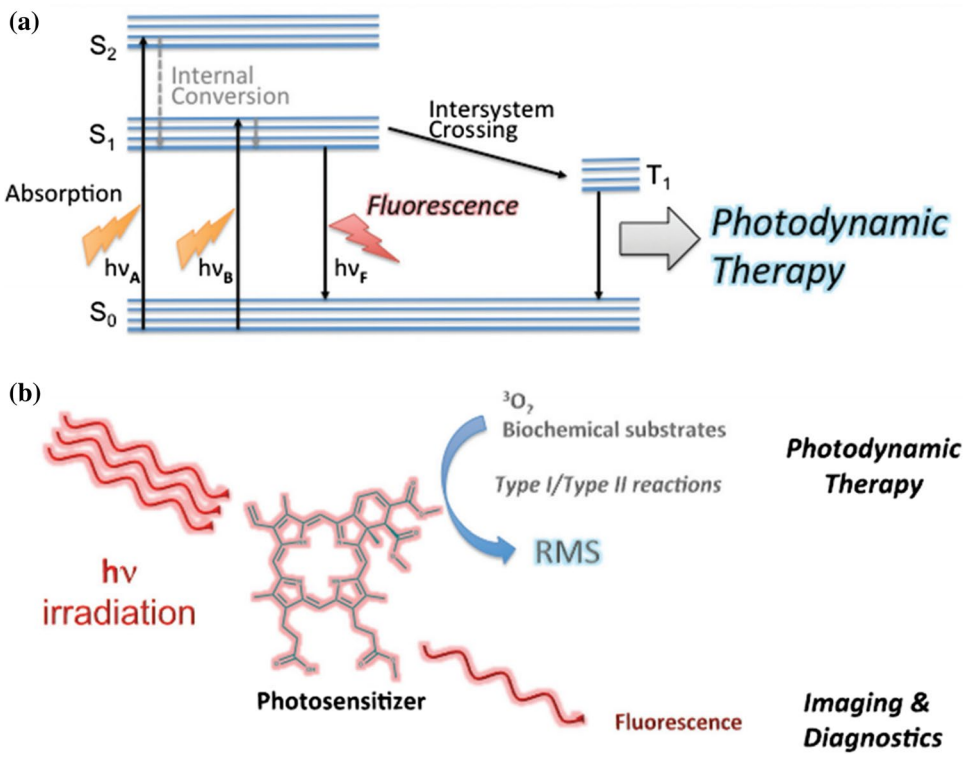


**Fig. 2** Schematic illustration of PDT mechanism. (Permission from RSC Pub)

biomolecules (e.g., protein, lipid, and nucleic acid) and intracellular organelles and destroy abnormal cells or microorganisms (Hwang et al. 2018). Additionally, the triggered ROS induce cell apoptosis or necrosis, damage the extracellular matrix and allow deeper penetration; PS can also be used as a tissue penetration enhancer (Kim et al. 2018b). Thus, advantageous PDT has been broadly utilized for not only cancer therapy but also therapy of various nonmalignant diseases: ophthalmic therapy, microorganism therapy and neovascular treatment (ho Hong and Choi 2018).

Most of the PSs have been developed to treat cancer, and the range of applications is widening. Some of them are already commercialized and on the market (Jeon and Ko 2019). However, presently commercialized PSs have several shortcomings that present challenges to their wide applications. For example, highly conjugated organic PSs including porphyrin, phthalocyanine, and chlorin derivatives are difficult to dissolve and present serious aggregation tendencies under physiological conditions, thus leading to unfavorable bioavailability and biodistribution (Li et al. 2018c). The lack of selectivity for lesion sites can lead to off-target side effects, such as hepatic spots and lytic necrosis. Moreover, uncontrollable photoactivity and slow clearance from the body could trigger post-treatment hazards such as risky photosensitization effects on eyes, skin and other normal tissues (Dolmans et al. 2003). To overcome the unfavorable characteristics of most PSs, smart nanoscale delivery systems were used. "Smart" refers to specific stimuli (e.g., pH, temperature, magnetic field, and light) responsive materials or multifunctionality for targeting specific lesions for increased therapeutic effect. The functional nanoparticles were studied and applied across fields of research for efficient, lesion-specific delivery of phototherapeutic agents without systemic toxicity. In this review, recent research and progress made in smart photodynamic nanomedicine for treatment of various diseases will be presented. Additionally, this summary provides past, present, and future perspectives on PDT.

## Photodynamic therapy with smart nanomedicine in cancer

As one application of PDT, PDT is regarded as a powerful cancer therapy tool due to its minimal invasiveness, clinical approval, and selectivity for the cytotoxicity of targeted cells by irradiation (Agostinis et al. 2011). In the late 1970s, the first PDT clinical study (Kelly and Snell 1976) was conducted using hematoporphyrin derivatives administered to 5 patients for treatment of bladder cancer. However, low selectivity to cancer cells and hydrophobicity of PS restricted its potential applications. To facilitate potential for cancer therapy, PS and their derivatives have been extensively studied by diverse approaches such as modification, which make them soluble in aqueous solvents and able to target cancer cells (Lee et al. 2014, 2013; Park et al. 2016b; Kim et al. 2015), fabrication of new materials for generating ROS (Youn et al. 2017; Guan et al. 2016), and incorporation within nanoparticles (Park et al. 2016a; Jeong et al. 2017). In this section, we will describe recent novel strategies of smart nanomedicine for cancer PDT. The strategies usually utilize the features of the tumor microenvironment such as hypoxia (Park et al. 2016b), enzymes (Lee and Na 2014), leaky vasculature (Kim et al. 2016; Park et al. 2015), and ligands for receptors overexpressed by cancer cells (Jo et al. 2019; Kim et al. 2015), etc.

Recently, Kim et al. (Kim et al. 2018b) developed tumor-penetrating trastuzumab (Tra) by chemically conjugating it with chlorin e6 (Ce6). Tra is applied for treatment of human epidermal growth factor receptor 2 (HER2) overexpressing cancer; approximately 30% of breast cancers overexpress this receptor (Mitri et al. 2012). Tra is a monoclonal antibody for receptor-ligand interaction which inhibits cellular growth and proliferation. Thus, Tra has shown efficient therapeutic effects on breast cancer, and the low penetration efficacy of Tra into tumors decreases the treatment response rates (only 12–35%) (Minchinton and Tannock 2006). In this regard, Ce6 was conjugated to Tra to achieve enhanced penetration due to the ROS generating ability of PS. Tra and Ce6 were coupled by using maleimide-poly(ethylene glycol)-Ce6 (TMPC, Fig. 3a), and the synthesis was confirmed with MALDI-TOF by demonstrating the changed mass compared to Tra. To evaluate the targeting ability of TMPC, it was used to treat breast cancer cell lines such as MDA-MB-231 (HER2-negative), SK-BR-3 (HER2-positive), MCF-7 (HER2-negative), and BT-474 (HER2-positive). On confocal images, Ce6 intensity was detected only for HER2-positive cell lines (SK-BR-3, BT-474), demonstrating the HER2 selectivity of TMPC. In addition, the tissue penetration was evaluated by TMPC treatment of frozen human breast cancer tissue. In comparison with Tra, the TMPC penetrated more deeply because of ROS, which can demolish dense tumor tissue (Fig. 3b).

The gastrointestinal (GI) tract, referred to as the alimentary canal, spans from the start at the mouth to the end at the anus. GI cancer usually occurs on the mucosal layer within the interior of the canal. With the improvement of flexible endoscopy, light sources are able to be reached directly to cancerous regions in the GI tract. The easy accessibility of lasers results in PDT's status as the most powerful tool for GI cancer treatment (Barr et al. 2001). GI cancer-related death is still the second leading cause of cancer death worldwide (Siegel et al. 2017). In this regard, Kim et al. (Kim et al. 2019) developed an Aptamer conjugated polymeric Ce6 for effective endo-laparoscopic PDT which can be practically used for GI cancer (Fig. 4a). To diagnose tumors of the GI tract, they visualized the cancerous lesions with an endoscopic device by using the Ce6 optical

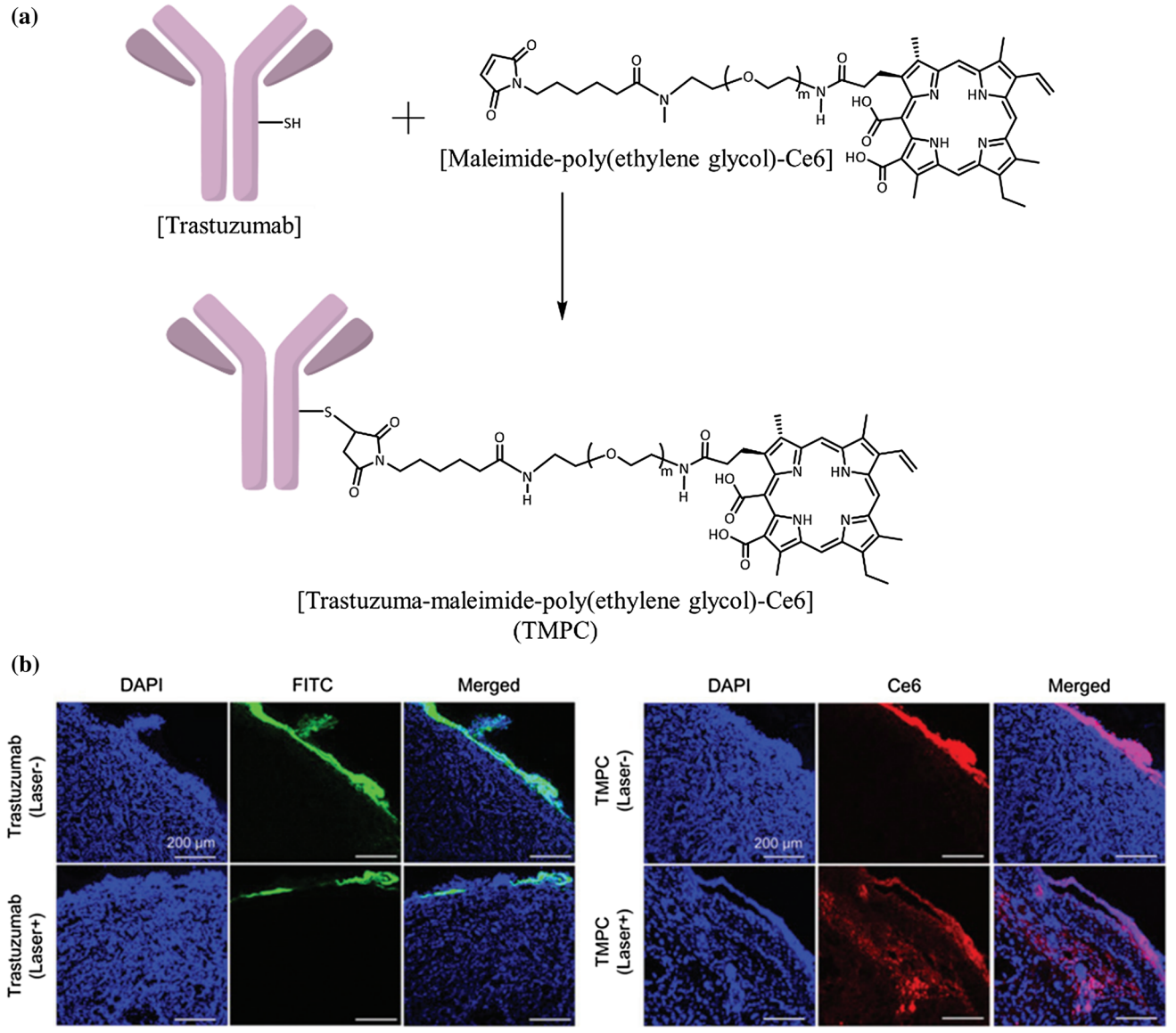


**Fig. 3** **a** Schematic illustration of TMPC synthesis route, and **b** immunohistochemistry images of human breast cancer tissue blocks. (Adapted with permission from Royal Society of Chemistry)

color of Aptamer-PEG-Ce6. In addition, then, the visualized cancer was irradiated with a laser from the device and treated due to the effect of PDT. Aptamer-PEG-Ce6 was composed of free Ce6, PEG, and Aptamer, AS1411, which is a single-stranded nucleotide interacting with nucleolin on cancer cells (Fig. 4b). Ex vivo tests were also conducted to diagnose nucleolin positive cancer. The xenografted tumor was extracted from mouse and then treated with PBS, PEG-Ce6, and Aptamer-PEG-Ce6. Only the Aptamer-PEG-Ce6 treated tumor showed a green signal in optical imaging and presented Ce6 fluorescence (Fig. 4c–e).

Han et al. (Han et al. 2018) prepared a tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) secreted from human mesenchymal stem cells (hMSCs) via photochemical internalization (TShMSC, Fig. 5a, b). TRAIL is a cancer protein drug that induces the process of cell death, called apoptosis. However, TRAIL has been restricted in clinical use due to its short half-life in blood circulation and low stability. To solve these problems, Han et al. tried to make TRAIL secreted by hMSC by transfecting the TRAIL gene into hMSC with a gene-polymer complex. Nevertheless, the inefficient transfection was still a major concern. In this regard, they introduced photochemical internalization (PCI). PCI, which is a gene delivery method, efficiently transfects genes through instant destabilization of the lipid bilayers of cells, endosomes, and lysosomes by ROS generation from

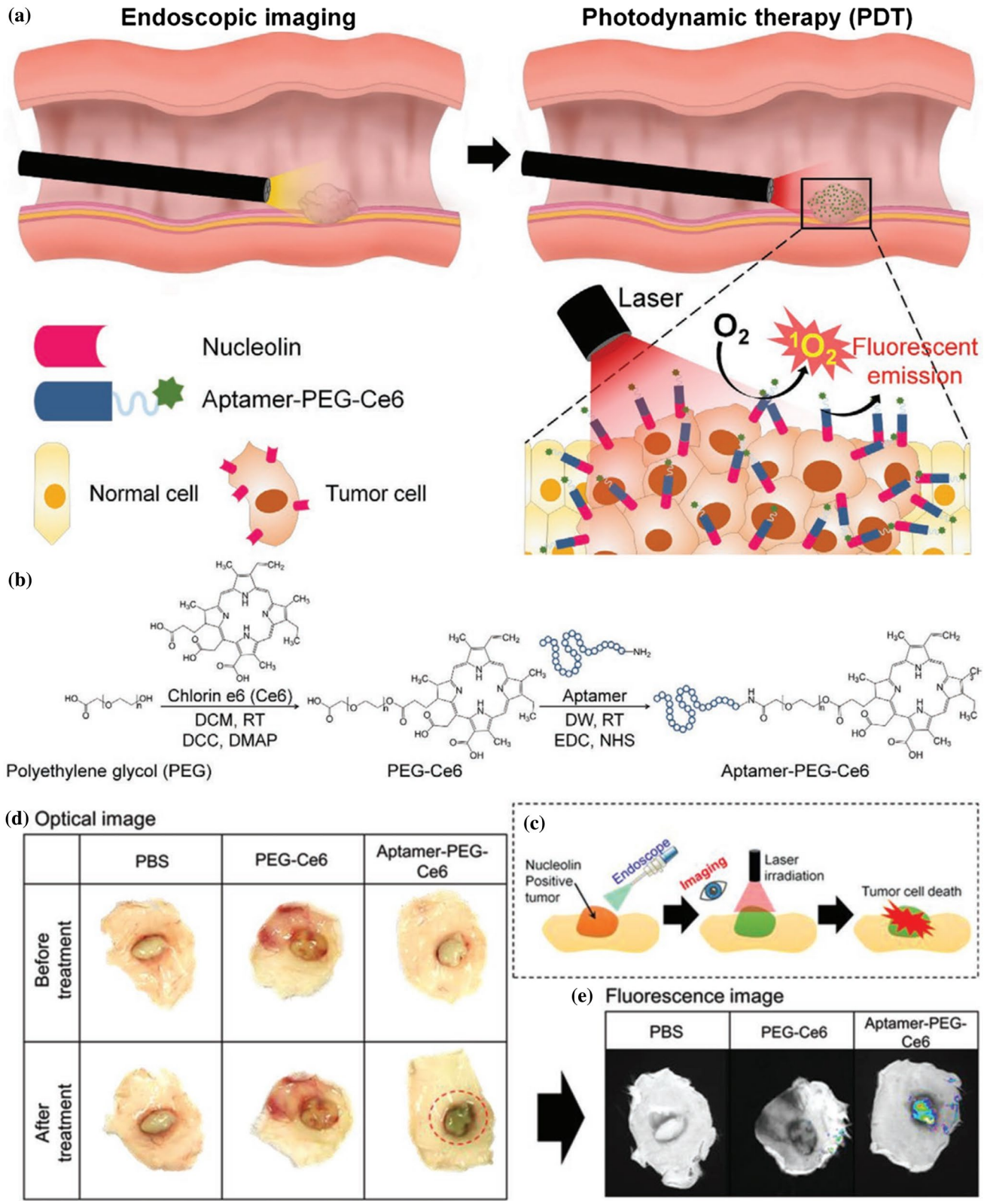


**Fig. 4** **a** Schematic illustration of Aptamer-PEG-Ce6 acting in nucleolin-overexpressed cancer, **b** synthesis route of Aptamer-PEG-Ce6, **c** schematic illustration of Aptamer-PEG-Ce6 imaging and PDT procedures, **d** optical images, and **e** fluorescence images after treatment with PBS, PEG-Ce6, and Aptamer-PEG-Ce6. (Adapted with permission from Elsevier)

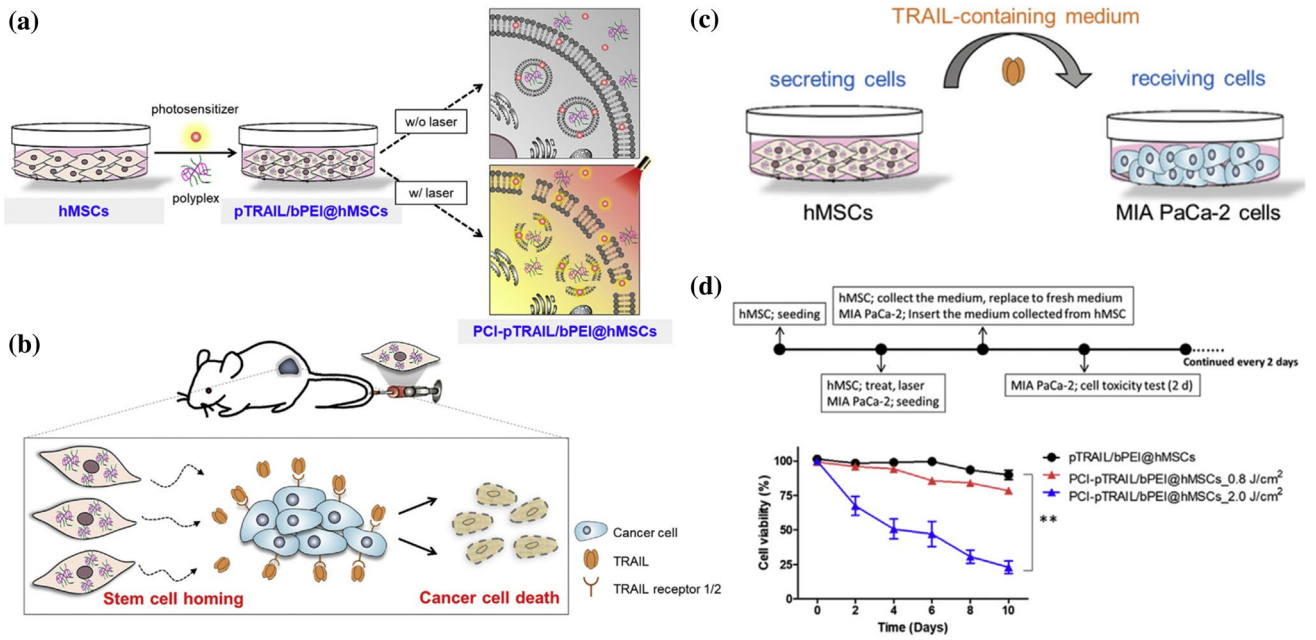


**Fig. 5** **a** Procedure of hMSC transfection with TRAIL gene/bPEI complex via PCI, **b** homing effect of engineered hMSC to cancer, **c** schematic illustration of hMSC media treatment method for in vitro testing, **d** cell viability of MIA PaCa-2. (Permission from John Wiley and Sons)

PS. First, they complexed the TRAIL gene with branched polyethyleneimine (bPEI), and the TRAIL polyplex was treated into hMSC with free pheophorbide A (PheoA). The TShMSC was harvested after laser irradiation. The TRAIL secreting ability of TShMSC was evaluated depending on laser power by flow cytometry and confocal microscopy. With increasing laser power, the TRAIL-expressing cell number was increased, and the intensity of TRAIL was detectable on the confocal images, indicating the expression of TRAIL in hMSC. Furthermore, to validate the therapeutic effect of TRAIL secreted from hMSC, TShMSC culture media samples were collected (Fig. 5c) every 2 days (0, 2, 4, 6, 8, and 10 days) and used to treat a pancreatic cancer cell line (MIA PaCa-2, Fig. 5d). Cell viability of MIA PaCa-2 decreased with the media treatment after 2 days.

Although studies for cancer therapy have been performed worldwide, cancer-related death remains an enormous problem and represents a large portion of human mortality. Smart nanomedicine could become a solution for these issues by more precise design of materials.

## Photodynamic therapy with smart nanomedicine in ophthalmic disease

For ophthalmologic disease therapy, local administration routes such as intravitreal, periocular, and subretinal injections are superior to systemic administration (Chang and Yeh 2012). However, repeated injections by these routes are inconvenient and cause fear in the patients, so steps for optimizing intravenous PDT are now being taken. In addition, PDT can be an efficient and innovative approach for curing neovascular diseases of the eye. Since FDA approval in 2000, ophthalmic PDT has been actively used by retinal specialists, and the most widely used photosensitive agent is verteporfin (Visudyne®), which is a benzoporphyrin derivative. Free benzoporphyrin derivative is very hydrophobic and easily aggregated in physiological conditions. However, Visudyne® is a liposomal formulation which enables effective dispersion of PS, and nanosized liposome can be retained in the neovascular region in the eye, which enables 'smart' lesion targeted therapy (Christie and Kompella 2008). Thus, the risk of vision loss in wet choroidal neovascularization (CNV) can be reduced. Additionally, choriocapillaris hypoperfusion and choroidal vascular remodeling can be induced with PDT after injection of verteporfin by resolving vascular hyperpermeability, extravascular leakage, and choroidal congestion (Lee et al. 2019). In this regard, ophthalmic PDT has also been selected as an effective approach in cases of benign vascular tumors and choroidal metastasis in ocular oncology (Fabian et al. 2017).

Among diverse ophthalmic diseases, PS is mainly used to treat wet age-related macular degeneration (AMD) caused by CNV, central serous chorioretinopathy (CSC), and polypoidal choroidal vasculopathy (PCV). CSC causes visual impairment and is characterized by leakage of fluid under the retina. When fluid is accumulated under the

central macula, the retina is detached and blurring or distortion of vision occur (Wang et al. 2008). After PDT, visual acuity may be reduced. PCV is characterized by an abnormal subretinal pigment epithelial network of vessels ending in polyp-like aneurysmal dilatations (Cheung et al. 2018). Hemorrhage and exudation from abnormal and leaky blood vessels can lead to serosanguineous detachment between the retinal pigment epithelium and retina. The AMD caused by these various conditions is the leading cause of blindness and decreases visual acuity in the elderly (Incorvaia et al. 2008). AMD can be divided into two types: dry AMD, which is called non-exudative AMD, and exudative, wet AMD. Abnormally formed blood vessels in wet AMD and related diseases are more fragile than normal blood vessels, which leads to blood and protein leakage in the subfoveal region. Continued bleeding and exudation from blood vessels cause permanent and irreversible damage to photoreceptors and vision acuity (Mitchell et al. 2018). If macular degeneration is suspected, distribution of neovascularization should be preferentially diagnosed. After that, the PS is intravenously injected and laser treatment is performed. The neovascularization can be eliminated without damage to the retinal nerve. The ROS generated following laser irradiation induce destruction of endothelial cells, abnormal blood vessel shutdown, decrease of blood flow, and vasoconstriction (Kliman et al. 1994; Zuluaga et al. 2007). The therapeutic effects of PDT have been demonstrated in many studies. The thickness of the CNV layer was decreased by narrowing of the dilated choroidal vasculature, and the subretinal fluid height was also decreased. Significantly, a selective occlusion of the choriocapillaris which reduced the exudation was observed without altering the inner choroidal layers (Chan et al. 2003; Lee et al. 2019). Various therapeutic modalities have been used for ophthalmic diseases, including laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor (VEGF), or PDT with verteporfin (Pointdujour-Lim et al. 2017). VEGF inhibitors such as ranibizumab and aflibercept have shown proper effects in improving visual symptoms. However, the VEGF inhibitor treatments combined with PDT were definitely preferable to monotherapy in improving visual outcomes (Koh et al. 2017).

The ophthalmic PDT offers distinct advantages in the clinic. However, as with other treatment modalities, repeated PDT treatments may lead to cumulative damage of the retinal pigment epithelium and retina. In addition, Visudyne® is not a suitable therapeutic agent for classic CNV with small lesions or occult CNV. In this respect, Visudyne® does not satisfy the perfect conditions for PDT. Therefore, diverse nanoscale platforms should be clinically applied as carriers to improve the disadvantages of PDT by utilizing the properties of nanoparticles. The smart nanocarriers incorporating PS can use lesion specific microenvironments and directly occlude diseased vascularization. In addition, nanocarriers functionalized with specific lesion targeting ligands can minimize damage to normal tissues. Additionally, as an alternative to the use of PS as PDT agent, PS mediated targeted delivery of therapeutic agents (e.g., drugs, genes, and dyes) can be effective for remedying neovascular disorders (Christie and Kompella 2008).

### Photodynamic therapy with smart nanomedicine for microorganism infection

Antimicrobial PDT has been developed since the 1990s. The advantages of PDT for antimicrobial use are the equal therapeutic effects regardless of the antibiotic resistance status (Vera et al. 2012) and the approach to the infected lesion, which is located externally, for laser irradiation. Although antibiotic resistance is regarded as a major concern for microbial therapies, PS did not show any resistance even after approximately 20 successive culture cycles of attack followed by regrowth (Maisch 2015). Likewise, novel strategies with smart nanomedicine for antimicrobial treatment having highly therapeutic potential are introduced in this section.

Acne is a skin disorder caused by *Propionibacterium acnes* (*P. acnes*) infection, and approximately 80–90% of the world population suffers from it. Antibiotics used for the treatment of acne, including tetracycline, erythromycin, and lincomycin, have been reported to induce skin redness, gastrointestinal disorders, diarrhea, sore mouth, liver toxicity, and vomiting. Importantly, antibiotic resistance is concerning as a major problem resulting from the use of antibiotics. In this regard, Park et al. (2016a) developed a lipase responsive transfersome (LRT, Fig. 6a, b). The LRT is a transformable liposome which can effectively pass through stratum corneum by a deformation and reformation process (Fig. 6c). When LRT meets *P. acnes* under the stratum corneum, the LRT is degraded by lipase, which is abundant within the acne infected lesion, and PS is exposed by degradation to exert PDT for antimicrobial effects. Because LRT exerts its antimicrobial effect only after degradation, it does not damage other regions except the acne lesion.

PDT for microorganisms does not induce genotoxicity, mutation, or resistance, which are important elements of microbial therapy. In addition to the abovementioned research, antimicrobial PDT has been actively introduced for use against dental diseases and skin diseases by using porphyrin, chlorin, and phthalocyanine derivatives.

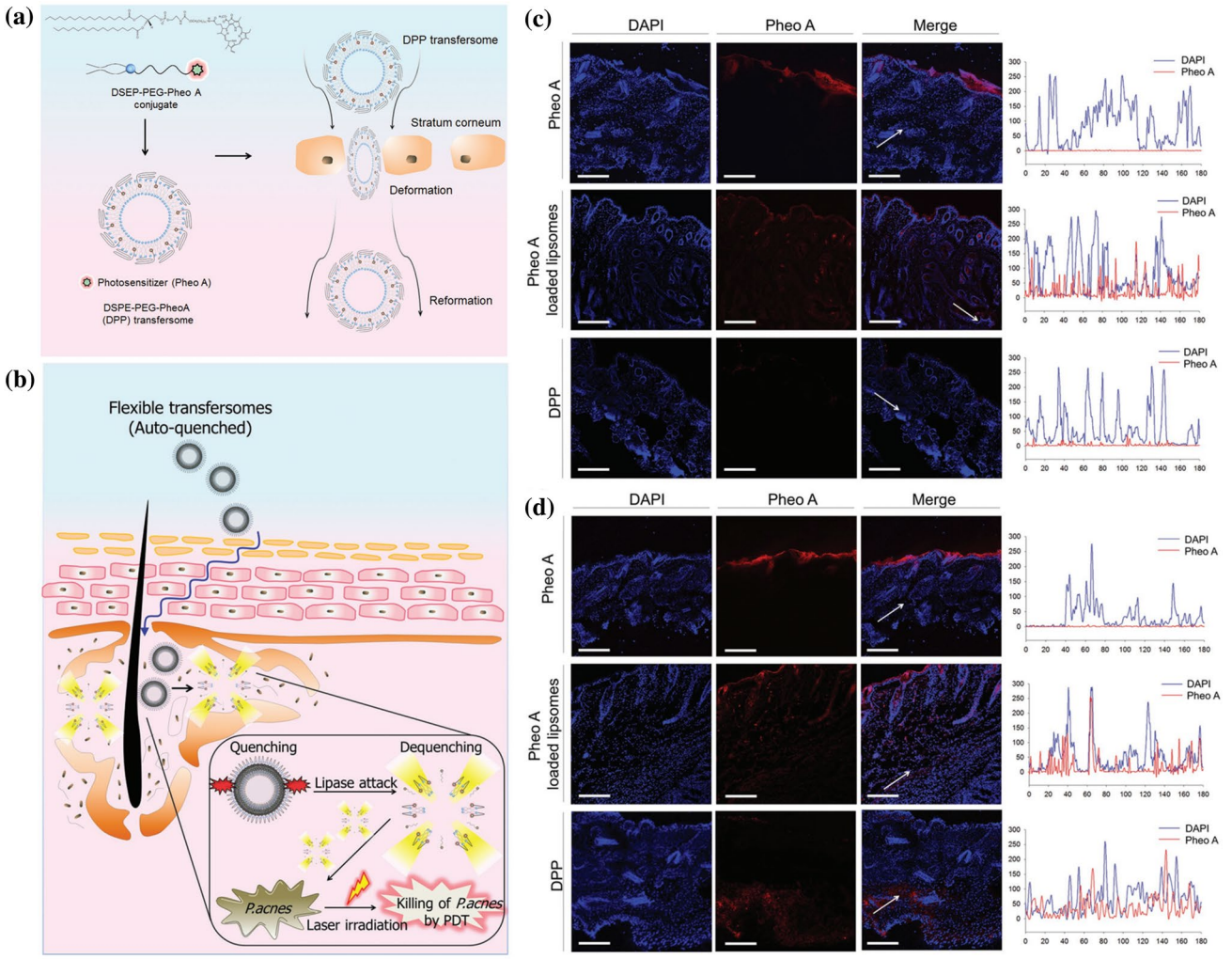


**Fig. 6** Schematic illustration of **a** skin penetration, and **b** lipase-responsive degradation of LRT, confocal microscopy image of Ce6 in (**c**) normal skin and **d** within an acne infected lesion. (Permission from John Wiley and Sons)

## Conclusion

The global market of PDT technology is projected to increase from 3.46 million dollars in 2016 to 4.36 million dollars in 2021. Steep growth has been shown in the USA, Asia and Europe, and the US market occupies 50% of the entire PDT market. As the scale of the PDT market grows, the number of PDT associated clinical trials is also increasing worldwide. During the last two decades, more than 400 clinical trials of PDT related to various diseases have been conducted and remain in progress. Due to its noninvasive property and spatiotemporal selectivity, PDT has become a clinically promising approach for the treatment of a wide range of diseases. Moreover, PDT which is mainly used for cancer therapy can be a useful way for immunotherapy in cancer treatment. Since conventional anticancer drug and radiotherapy destroy normal cells as well as immune cells, they can induce suppression of whole immune system in patients. However, PDT can trigger topical immune response by releasing tumor associated antigen and activating immune cells and it can block the metastasis and relapse of cancer.

Various PSs have now been approved in the USA, Asia, and Europe, and PDT is clinically applied to cure various diseases (Agostinis et al. 2011; Baskaran et al. 2018). Recently, the demands for photodynamic diagnosis and therapy have tended to increase as the medical paradigm changes to "minimally invasive treatment". However, PDT is still considered as an alternative or supporting remedy due to its limitations, primarily including low tissue penetration by light and inaccurate lesion selectivity by PSs (Abbas et al. 2017). For these reasons, diverse nanoscaled delivery platforms have been developed, and ideal phototherapeutic nanomaterials should possess the following characteristics: (1) biocompatibility and biodegradability without toxicity and undesirable immunogenicity; (2) stability in physiological conditions, and cancer specific targeting and

accumulation; (3) strong NIR absorption for efficient and sufficient light absorbance; (4) large singlet oxygen quantum yield for PDT. With improvement of these mentioned features, PDT has the potential to become a primary therapy, depending on the specific indication and to revolutionize therapeutic strategies (Choi et al. 2017). It is expected that PDT will continue to be used as a stand-alone modality or used in combination with chemotherapy or surgery. In addition to the therapeutic aspects of PDT, photodynamic diagnostic imaging using fluorescence has assumed an important role in the study of the biodistribution and pharmacokinetics of therapeutics (Li et al. 2018a). Enabling personalized dosimetry and real-time monitoring will provide opportunities for individualized therapy and the enhancement of treatment procedures and impact healthcare costs. Consequently, this approach can fulfill the vision of personalized medicine in the near future.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no conflict of interest.

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