Clinical development and potential of photothermal and photodynamic therapies for cancer

Xingshu Li[1], *Jonathan F. Lovell*[2]✉, *Juyoung Yoon*[3]✉ *and Xiaoyuan Chen*[4]✉

Abstract | Light-activated, photosensitizer-based therapies have been established as safe modalities of tumour ablation for numerous cancer indications. Two main approaches are available: photodynamic therapy, which results in localized chemical damage in the target lesions, and photothermal therapy, which results in localized thermal damage. Whereas the administration of photosensitizers is a key component of photodynamic therapy, exogenous photothermal contrast agents are not required for photothermal therapy but can enhance the efficiency and efficacy of treatment. Over the past decades, great strides have been made in the development of phototherapeutic drugs and devices as cancer treatments, but key challenges have restricted their widespread clinical use outside of certain dermatological indications. Improvements in the tumour specificity of photosensitizers, achieved through targeting or localized activation, could provide better outcomes with fewer adverse effects, as could combinations with chemotherapies or immunotherapies. In this Review, we provide an overview of the current clinical progress of phototherapies for cancer and discuss the emerging preclinical bioengineering approaches that have the potential to overcome challenges in this area and thus improve the efficiency and utility of such treatments.

Chromophores
Light-absorbing molecules that impart colour.

[1]*College of Chemistry, Fuzhou University, Fuzhou, China.*

[2]*Department of Biomedical Engineering, State University of New York at Buffalo, Buffalo, NY, USA.*

[3]*Department of Chemistry and Nanoscience, Ewha Womans University, Seoul, Republic of Korea.*

[4]*Laboratory of Molecular Imaging and Nanomedicine (LOMIN), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health (NIH), Bethesda, MA, USA.*

✉*e-mail: jflovell@buffalo.edu; jyoon@ewha.ac.kr; shawn.chen@nih.gov*

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Phototherapy, which involves the exposure of patients to light in order to treat disease, has been documented for thousands of years, with examples from ancient Indian, Chinese and Egyptian civilizations of sunlight being exploited to treat diseases such as psoriasis, vitiligo and skin cancer[1]. In 1900, the cytotoxic effects of combining acridine dyes with light exposure were demonstrated[2]. Around the same time, Niels Ryberg Finsen was using red light to treat smallpox and blue light to treat cutaneous tuberculosis (lupus vulgaris)[3], work for which he was awarded the Nobel prize in Medicine and Physiology in 1903. The advent of the laser by Theodore H. Maiman[4] in 1960 as a light source that emits photons in a coherent and narrow beam has profoundly shaped phototherapy. One of the first applications of lasers in surgery was demonstrated by ophthalmologists in 1963 for the photocoagulation of detached retinas[5]; shortly thereafter, lasers were evaluated for tumour ablation, exploiting their high energy to induce heating and thus cell damage[6]. However, laser therapy for tumour ablation has important limitations, including the non-selectivity towards malignant cells owing to the presence of endogenous chromophores in non-malignant tissues and the requirement for a high power density; thus, with high-energy laser light, the specific targeting of cancer cells while sparing non-malignant cells is possible only through precisely localized light irradiation. In addition, to efficiently induce tumour ablation, high-power lasers — up to hundreds of watts[7] — are required, which introduces safety and logistical concerns. Accordingly, phototherapies that involve the administration of exogenous photosensitizing agents to enhance the therapeutic effects of light radiation have been developed, including photodynamic therapy (PDT) and photothermal therapy (PTT). Owing to efficient light absorption of the administered agents, this approach enables phototherapy using lower power densities. In general, PDT is a lower-power modality than PTT (in typical clinical PDT protocols, laser fluences of 50–100 J/cm^2 are used). Thus, the combination of a photosensitizer with light is an efficient approach for tissue destruction based on chemical damage induced by the photosensitized reactions rather than on heating. The primary selectivity in both these forms of phototherapies comes from control of the volume of illumination of particular tissues, focusing on the target tissue (for example, the tumour). A second level of selectivity is provided by the preferential localization of the light-absorbing photosensitizers and chromophores, exogenous or endogenous, to the target tissue.

Key points

- Photodynamic therapy is predicated on the localized activation of photosensitizers within tumours in order to induce chemical damage and thus the death of tumour cells; this approach has been used in the clinic for >40 years for the treatment of diverse cancers, including superficial skin lesions and oesophageal and lung tumours.
- Photothermal therapy (PTT) agents, which can be used to increase the efficiency of localized light-based heating and ablation of tumour tissues, have not yet been tested in large clinical trials; laser ablation without PTT agents has been used clinically.
- Relative to single-modality approaches, drug–device combinations complicate clinical development; therefore, compelling efficacy and safety benefits are needed to support the use of such platforms in favour of competing ablative therapies.
- Novel preclinical phototherapy agents have been engineered with advanced targeting and activation mechanisms.
- These next-generation molecules and nanomaterials hold the potential to reduce adverse effects and/or improve the effectiveness of photodynamic therapy and PTT, leading to better outcomes and increased clinical adoption.

In clinical settings, photosensitizing agents are usually administered through intravenous or topical application, although other delivery routes are possible, including oral delivery (for example, of aminolevulinic acid (ALA)), which is more convenient for patients but is associated with concerns over inter-patient variability in bioavailability and pharmacokinetics. In preclinical studies in rodents, the pharmacokinetics and biodistribution of photosensitizers has been shown to differ depending on whether they are administered intraperitoneally or intravenously[8]. After a variable time interval following administration of the photosensitizer, light of a fixed wavelength is specifically focused on the site of the target lesion, leading to selective excitation of the photosensitive agents and to the subsequent induction of photophysical and photochemical actions for cancer treatment (FIG. 1a).

In PTT, photothermal agents enhance the heating of cells and tissues in the local area. When these agents are irradiated by light of a specific wavelength, they absorb energy from photons and are transformed from their ground singlet state to an excited singlet state. The electronic excitation energy then undergoes vibrational relaxation, a non-radiative form of decay, whereby a return to the ground state is mediated by collisions between the excited photothermal agents and their surrounding molecules. Consequently, increased kinetic energy leads to heating of the surrounding microenvironment (FIG. 1b). When the temperature of a tissue is increased to 41 °C, a heat-shock response is initiated that in turn induces a series of rapid changes in gene-expression patterns, including the generation of heat-shock proteins, to mitigate the effects of the initial thermal damage[9]. When the temperature increases to 42 °C, irreversible tissue damage occurs; heating of tissues to a temperature of 42–46 °C for 10 min results in cell necrosis[10]. At 46–52 °C, cells die rapidly owing to microvascular thrombosis and ischaemia. At tissue temperatures >60 °C, which are usually achieved with PTT, cell death is almost instantaneous owing to protein denaturation and plasma membrane destruction[10].

Unlike PTT, PDT is predicated on the generation of reactive oxygen species (ROS) to induce cytotoxic effects. PDT requires three components: a photosensitizer, molecular oxygen and light. Upon irradiation, photon absorption by the photosensitizer leads to an excited electronic state. The excited singlet state of the photosensitizer can then undergo intersystem crossing to generate a long-lived excited triplet state and relaxation, with energy emitted as fluorescence, heat and/or other forms of photophysical energy. The excited triplet state subsequently promotes the generation of ROS through two mechanisms: in the type I pathway, the photosensitizer participates in electron transfer reactions to produce radicals and radical ions whereas, in the type II pathway, the photosensitizer transfers energy to triplet ground-state molecular oxygen ($^3O_2$), thus generating highly reactive singlet oxygen ($^1O_2$)[11–13].

Efficient photothermal agents should have high levels of light absorption at the treatment wavelength, a high photothermal conversion efficiency and photostability, minimal 'dark toxicity' (outside of the light-exposed tissues) and good biocompatibility. Photothermal agents for potential anticancer applications can be classified into several types: organic dye molecules (for example, indocyanine green and heptamethine cyanine), organic nanoparticles (such as porphyrin–lipid conjugate porphysome and organic semiconducting polymer nanoparticles), noble metal materials (particularly gold nanoparticles), carbon-based materials (such as graphene oxide and carbon nanotubes) and other inorganic materials (including quantum dots and metal oxide nanoparticles)[14–16].

Hundreds of photosensitizers have been applied clinically or preclinically for PDT, including porphyrin, chlorin or phthalocyanine derivatives, all of which have tetrapyrrole structures[17–19]. This macrocycle structure is associated with efficient light absorption and singlet oxygen generation. Additionally, methylene blue, Rose Bengal and hypericin have been utilized as photodynamic agents in clinical applications or trials[20,21]. Many other photoactive agents, such as boron-dipyrromethene and cyanine dyes, fullerenes, semiconductors and aggregation-induced emission fluorogens, have photodynamic properties conducive to oncological applications[22–25]. Besides the selection of a photosensitizer, the mode of light application and drug–device combinations add layers of complexity to PDT; the numerous parameters to be considered include the light source (for example, laser, light-emitting diode (LED) or controlled sunlight exposure) as well as irradiation parameters (such as the wavelength, fluence rate and total fluence), the photosensitizer dose, the interval between drug administration and light application, and the irradiation geometry. Therefore, PDT dosimetry is a complex but important topic[26].

Most PTT and PDT agents absorb light in the visible range (wavelengths of 400–700 nm) or near-infrared (NIR) range (700–1,350 nm). Suitable lasers are commercially available to excite these agents, including diode lasers (630–1,100 nm), dye lasers (390–1,000 nm), alexandrite lasers (720–800 nm) and neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers (1,064 nm)[27]. NIR light sources can also be created by optical parametric amplification or oscillation. For example, tunable 900–1,300 nm NIR light sources can be generated using

Photosensitizers
Chromophores that generate reactive oxygen species upon irradiation.

Singlet state
A molecular quantum state in which all the electron spins are paired.

Triplet state
A molecular quantum state in which an excited electron spin is unpaired.

Fluence rate
The radiant energy incident per second crossing a sectional area of an irradiated spot, equating to the light power transferred per unit area, for example, in W/cm^2 (1 W = 1 J/s).

Total fluence
The total energy of light crossing a sectional area of an irradiated spot (exposed light energy per unit area, J/cm^2).

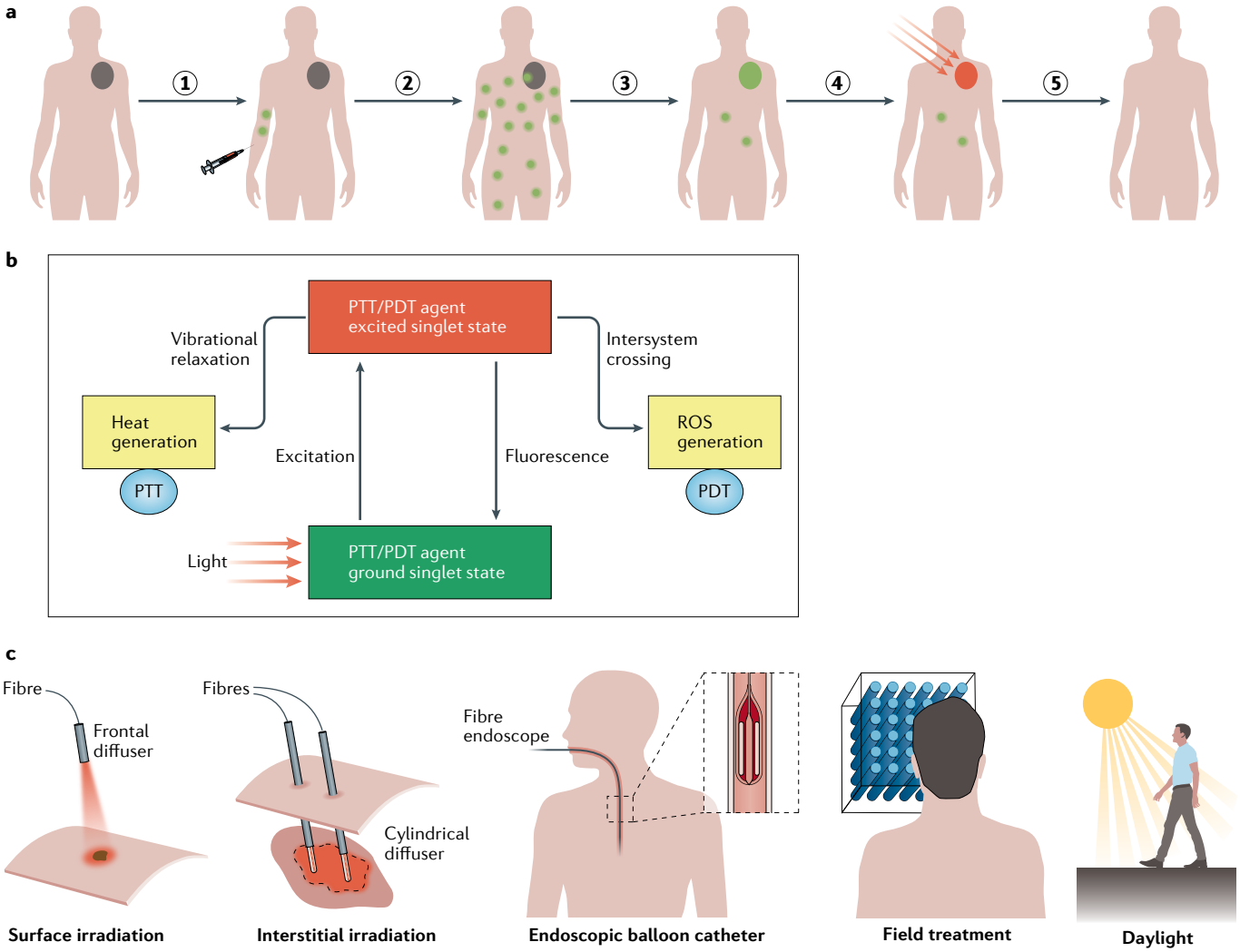

Fig. 1 | **General procedure and mechanisms of action for PTT and PDT.** **a** | (1) The photothermal therapy (PTT) or photodynamic therapy (PDT) agent (photosensitizers; small green circles) is administered to the patient, typically intravenously. (2) The PTT and/or PDT agent is subsequently distributed around the body. (3) Accumulation of PTT or PDT agent in tumour tissues (indicated by previously grey ovals, representing the tumour, turning green) can be achieved through active and/or passive targeting strategies and optional molecular activation exploiting, for example, proteases or hypoxia in the tumour microenvironment. (4) Local application of light of a specific wavelength to the tumour tissues results in excitation of the PDT or PTT agent from a ground singlet state to an excited singlet state (indicated by red oval). (5) Tumour ablation following excitation of the PTT or PDT agent results predominantly from thermal and chemical damage, respectively. **b** | Thermal damage is caused by heat released during vibrational relaxation of the excited PTT agent, whereas chemical damage is caused by reactive oxygen species (ROS) generated through energy and/or electron transfer from the PDT agent after intersystem crossing of the excited singlet state to a longer-lived triplet state. **c** | Common light delivery paradigms used for clinical phototherapy in oncology. Various approaches are available and can be tailored to the location and extent of the tumour. The accumulation of a photosensitizer in target tumours is a pre-requisite for PDT. Light penetration of tissues is highly limited and thus interstitial light delivery using multiple fibres is required for the treatment of large and/or deep-seated tumours.

a green laser (≈532 nm) as a source to 'pump' photons to a longer wavelength. Light irradiation of target tissue can be achieved by a variety of methods, including the use of frontal diffuser fibres for surface irradiation[28], multiple cylindrical diffusing fibres for interstitial light delivery into large and deep-situated tumours[29], and balloon catheters for irradiation of oesophageal tissues[30]; for topical PDT treatments, the use of LED arrays[31] for the treatment of large areas of skin has been established, as has the use of controlled exposure to natural daylight[32] (FIG. 1c).

PDT and PTT have unique capabilities compared with those of other ablative modalities used in the treatment of cancer (such as surgery, cryoablation, microwave ablation, radiofrequency ablation and brachytherapy). The use of photosensitizers that accumulate in cancerous tissues provides a degree of additional treatment selectivity. The control of light placement further minimizes off-target toxicity to surrounding tissues. Interventional techniques with optical fibres and endoscopy can be used to avoid laparotomy and thoracotomy. PDT results in minimal scarring not least because photosensitizers do not tend to accumulate in connective tissue[33]. PDT treatments can also safely be applied multiple times, although resistance mechanisms have been identified[34].

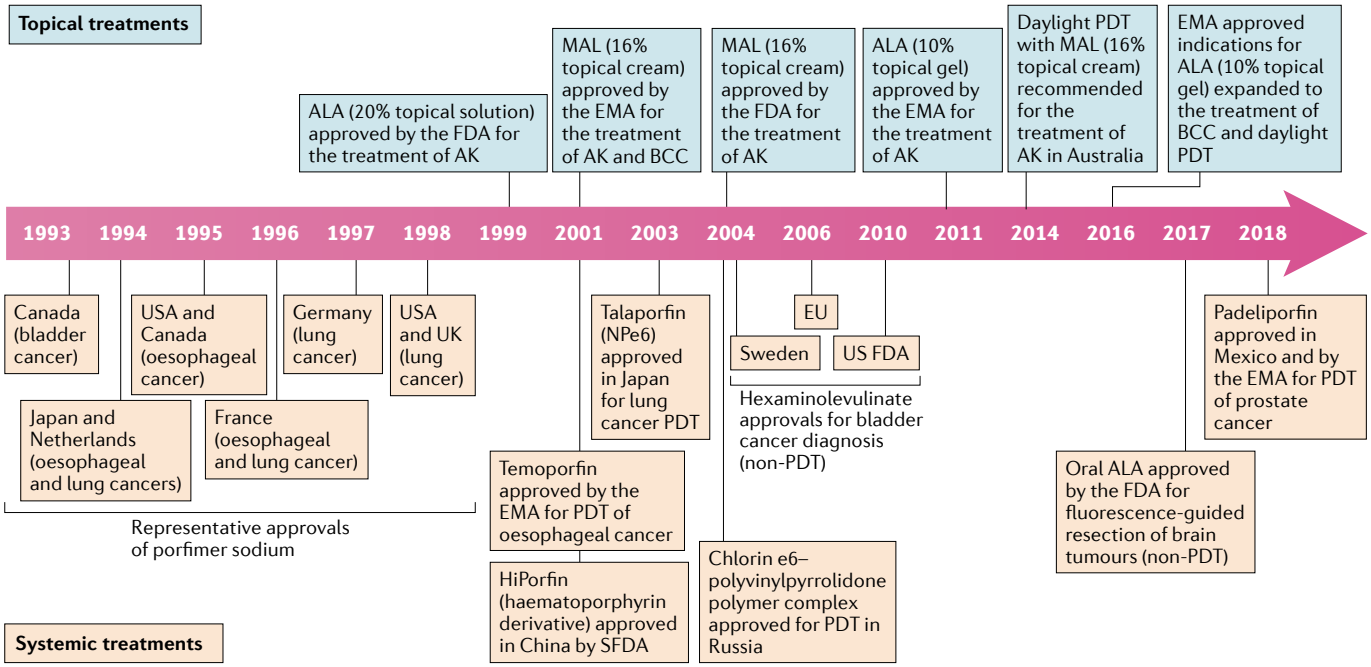

Fig. 2 | **Timeline of select approvals of PDT photosensitizers for cancer indications.** The timeline shows a non-exhaustive list of regulatory approvals of various photosensitizers in indicated jurisdictions. Oral aminolevulinic acid (ALA) and hexaminolevulinate are approved for photodiagnosis but not for photodynamic therapy (PDT). Actinic keratoses (AKs) are not cancerous per se but, in some patients, can progress to squamous cell carcinoma. BCC, basal cell carcinoma; MAL, methyl aminolevulinate; SFDA, State Food and Drug Administration (now known as the National Medical Products Administration).

Notably, PTT and PDT have considerable potential to be used in combination with other therapeutic modalities such as chemotherapy[35] and immunotherapy[36]. Herein, we discuss the clinical advances in PTT and PDT for the treatment of cancer as well as challenges in the application of these therapies, emerging bioengineering solutions and future directions for phototherapy.

Clinical progress with PDT and PTT

PDT in oncology

Overview. Precancerous keratosis skin lesions and some non-melanoma skin cancers are commonly treated with PDT in clinical practice[37]. In addition, several solid tumour types, including oesophageal, lung and prostate cancers, have been shown to be viable targets for PDT in selected patients[38]. PDT also holds potential as a treatment option for many other tumour types, with supportive evidence from clinical trials for cancers of the breast, head and neck, bile duct, bladder, pancreas, cervix, brain and other organs[38].

PDT has been used to treat cancer in the clinic for more than 40 years. In 1978, Dougherty et al.[39] reported that intravenous injection of a photosensitizer termed 'haematoporphyrin derivative' (HpD), consisting of a complex mixture of water-soluble porphyrin monomers and oligomers, enabled a range of cutaneous and subcutaneous tumour types to be effectively ablated with red light irradiation using an argon dye laser. As early as the 1950s, HpD had been shown to accumulate in neoplastic tissues in humans, thus providing a means of photodiagnosis[1]. PDT has subsequently been tested and approved by regulatory agencies worldwide for several cancer indications[40], with approved indications encompassing both skin lesions and solid tumours steadily increasing over the past decades (FIG. 2).

Porfimer sodium, a purified component of HpD, is the most commonly used photosensitizer for PDT of non-cutaneous solid tumours. In 1993, porfimer sodium was granted regulatory approval for PDT of bladder cancer in Canada, followed by FDA approval in 1995 for symptom palliation in patients with obstructing oesophageal cancer and in 1998 for non-small-cell lung cancer (NSCLC) indications[41] (FIG. 2). HpD was granted approval in China for oncological indications in 2001 (REF.[42]). In 2003, the FDA also approved this agent for PDT of precancerous high-grade dysplasia in patients with Barrett oesophagus[43]. Despite these approvals, the sales revenues for porfimer sodium suggest that PDT is not widely used in the treatment of solid tumours[44]. Technological advances to increase the safety and efficacy of PDT and to broaden its indications as well as to perhaps increase the awareness of and familiarity with the use of this technique among physicians are key avenues for expanding the use of PDT in the treatment of solid tumours.

Porfimer sodium has the advantages of being well tolerated at current clinical doses and of being soluble in water without the need for solubilizing excipients; however, its drawbacks include increased skin photosensitivity and thus a risk of cutaneous toxicities upon prolonged exposure to sunlight[45], its complex oligomeric composition and its limited absorption of red light. The peak of the porfimer sodium absorption spectrum is in

the range of blue–violet light (405 nm), which has limited penetration of biological tissues owing to light scattering and absorption by endogenous chromophores in tissue. Nevertheless, porfimer sodium can be excited with red light, and laser light of ~630 nm is used for porfimer sodium-based PDT. So-called second-generation photosensitizers that have been granted regulatory approval in some jurisdictions for cancer therapy, such as temoporfin, talaporfin and padeliporfin (FIG. 2), are chemically pure compounds of the chlorin and bacteriochlorin class (reduced porphyrin structures), which better absorb red or NIR light. This characteristic results in a higher PDT efficiency, thus lowering the required photosensitizer doses, which in turn reduces the duration of photosensitivity.

Several other photosensitizers have reached the clinical stages of development, some of which have achieved clinical approval in China and Russia for the treatment of cancer. These agents include 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a, silicon phthalocyanine 4, redaporfin (a bacteriochlorin), hemoporfin (haematoporphyrin monomethyl ether), photosens (a mixture of sulfonated aluminium phthalocyanines), photocyanine (a zinc phthalocyanine), photodithazine (a chlorin e6 derivative), radachlorin (a chlorin and purpurin mixture) and chlorin e6 sodium-polyvinylpyrrolidone (photolon; a chlorin e6 derivative formulation)[46–48]. Verteporfin, which is approved for use to treat macular degeneration by PDT, has also been re-purposed in early phase oncology clinical trials, including for the treatment of vertebral metastases[49]. Other trials of verteporfin have included patients with breast cancer, pancreatic cancer and pleural malignancy, with results pending (NCT02872064, NCT02939274, NCT03033225 and NCT02702700).

Worldwide, dozens or hundreds of clinical trials have evaluated PDT for solid tumours[50], although only a few large-cohort trials in a narrow range of malignancies have been reported. In the following sections, we describe the progress made in PDT for indications that have been the focus of clinical testing and regulatory approvals, including oesophageal, lung, head and neck, and skin cancers, as well as several emerging indications.

Oesophageal cancer. Oesophageal cancer accounted for approximately half a million deaths worldwide in 2018 (REF.[51]). This disease has been a long-standing target for PDT[52]. Surgical oesophageal tumour resection by oesophagectomy carries risks of postoperative complications[53], thus PDT and other local treatment techniques are appealing. Endoscopic light delivery fibres and catheters with cylindrical diffusers and centring balloons enable the uniform irradiation of target dysplastic or neoplastic lesions on the oesophageal wall and are commercially available (FIG. 1c).

Results of a randomized controlled study comparing porfimer sodium PDT to Nd:YAG laser ablation in 218 patients with advanced-stage oesophageal cancer and dysphagia were reported in 1995 and demonstrated a higher objective tumour response rate with PDT (32% versus 20% at 1 month; $P < 0.05$)[54], although the improvements in dysphagia were similar with both treatments. Endoscopic PDT with porfimer sodium for the palliative treatment of oesophageal obstructions has also been assessed retrospectively in a series of 215 patients[55]. In total, 318 courses of PDT were administered and resulted in effective symptom palliation in 85% of patients (in terms of mean dysphagia scores); PDT was most effective for endoluminal obstructions[55]. In another study[56], 104 patients with squamous cell carcinomas and 19 with adenocarcinomas underwent curative-intent PDT of small oesophageal tumours (mostly uT1 or uT2) using HpD and a fibrescope, resulting in a complete response (CR) rate of 87% at 6 months; the 5-year disease-specific survival was 74%. In 102 patients with Barrett oesophagus and high-grade dysplasia or mucosal adenocarcinoma, 56% had complete ablation of the glandular epithelium with a single course of porfimer sodium PDT; however, stricture requiring dilation occurred in 20% of patients[57]. Furthermore, in a multicentre randomized phase III trial evaluating the addition of porfimer sodium PDT to proton-pump inhibitor therapy using omeprazole in with patients with Barrett oesophagus and high-grade dysplasia[58], 106 of 138 (77%) patients had complete eradication of high-grade dysplasia at any time during the study period as compared with 27 of 70 (39%) with omeprazole alone; 13% versus 28% of patients developed oesophageal adenocarcinoma ($P < 0.006$). Photosensitivity reactions and oesophageal strictures were the most common serious adverse events (AEs) associated with PDT.

Photosensitizers other than porfimer sodium have also been used in the treatment of oesophageal cancers. In a comparative study with results reported in 2018 (REFS[59,60]), patients with neoplasia associated with Barrett oesophagus underwent PDT with either intravenous porfimer sodium or oral ALA. No significant differences in complete reversal of intestinal metaplasia and of dysplasia were observed between the treatment arms (78% versus 63% ($P = 0.18$) and 90% versus 76% ($P = 0.26$), respectively, at a median follow-up duration of 67 months). Talaporfin PDT has been tested in a phase I trial involving nine patients with local progression of oesophageal cancer after radiotherapy or chemoradiotherapy[61], resulting in five CRs and no phototoxicity. More recently, results of a multicentre phase II trial in 23 patients demonstrated that talaporfin PDT induced a CR in 89% of patients without skin phototoxicity or severe AEs.

Despite several reports of clinical activity against oesophageal dysplasia and tumours over the past 35 years, PDT has lost favour in clinical practice owing, in part, to the lower effectiveness of this approach relative to other endoscopic techniques, including endoscopic submucosal dissection, radiofrequency ablation and cryotherapy[62]. Treatment site-specific PDT complications, such as strictures that often require balloon dilation intervention, are another reason explaining the preference for other treatment modalities. In a randomized study involving 60 patients with Barrett oesophagus receiving PDT for dysplasia or early stage cancer, oral prednisone was administered with the aim of preventing strictures[63]; however, the incidence of strictures was increased with prednisone treatment (29% versus 16% with PDT alone).

Lung cancers. Lung cancers are responsible for 18.4% of all cancer-related deaths[51]. PDT has been applied in the treatment of various forms of lung cancer[64], and porfimer sodium PDT is FDA approved for the ablation of microinvasive endobronchial NSCLCs not suitable for other treatments and of completely or partially obstructive endobronchial NSCLC.

Many studies of PDT for lung cancer have been carried out in Japan, where activity in this area has been ongoing since 1980 (REF.[60]). In 1985, results of a study conducted in the USA showed that PDT treatment of endobronchial blockages in patients with obstructing lung cancer induced a CR in 20 of 22 patients (91%)[65]. In addition, a prospective study in 100 patients with advanced-stage inoperable bronchopulmonary cancer revealed that PDT with porfimer sodium could effectively relieve obstructive endoluminal malignant lesions[66]. PDT can also be combined with external beam radiotherapy, potentially resulting in better and longer lasting control of NSCLC-related endobronchial obstructions[67]. Results of a randomized controlled study reported in 1999 pointed to benefits of PDT compared with Nd:YAG laser thermal ablation for treating tracheobronchial obstructions in patients with inoperable NSCLC[68]. Patients in both groups had symptom relief, but those in the PDT group had a longer median time until treatment failure (50 days versus 38 days; $P = 0.03$) as well as a longer median overall survival (OS) duration (265 days versus 95 days; $P = 0.007$).

Bronchoscopy can be integrated with PDT to position the light fibre within the bronchi for tumour irradiation in patients with NSCLC. Tumours situated near the central bronchi are usually targeted because manoeuvring the bronchoscope into distant secondary bronchi is challenging. In patients with early stage NSCLC, PDT can induce CRs but disease recurrence often occurs. In a phase II study involving 54 patients treated with porfimer sodium PDT, a CR was observed for 50 of 59 evaluable tumours (85%)[69]. The longitudinal extent of the tumour was independently prognostic of treatment outcome (a CR)[69], with optimal activity in patients with tumours ≤1 cm in diameter. In a study involving 240 patients with bronchogenic carcinoma treated with porfimer sodium PDT over a decade-long period, a CR was achieved in 40% of lesions[70]. Outcomes were more favourable in patients with early stage lesions, with CRs in 83%. Another study, involving 93 patients, revealed that 10% of early stage lung cancer lesions recurred after a CR to PDT, attributed to incomplete ablation with residual tumour cells[71].

Talaporfin, also known as NPe6, has been approved in Japan since 2004 for the treatment of early stage endobronchial cancer[72] (FIG. 2). A phase II study of talaporfin was conducted in 41 patients with a total of 46 superficial lung squamous cell carcinoma tumours <2 cm in diameter, and a CR was observed for 85% of evaluable lesions (in 83% of patients)[73].

Beyond centrally located tumours accessible by bronchoscope, lung tumours situated further from the bronchus can be treated with PDT using a different light-delivery approach. In one study[74], 19-gauge needles containing an internal catheter were inserted percutaneously into early stage peripheral lung tumours under CT guidance followed by extraction of the needles and placement of a diffuser fibre with a tip 2 cm long for light delivery into the tumours via the catheter. Seven of the nine patients treated achieved partial remission with this approach to porfimer sodium PDT[74], although two patients had pneumothorax.

Malignant pleural mesothelioma (MPM) is a lethal cancer that develops in the outer lining of the lungs. PDT is an attractive option for treating MPM because the disease tends to be located on the pleural surface and is thus amenable to the delivery of light[64]. However, in a small-cohort phase III study involving 63 patients with MPM, the addition of intraoperative porfimer sodium PDT to surgery followed by immunochemotherapy with cisplatin, IFNα-2b and tamoxifen did not improve local control or survival outcomes[75].

Head and neck cancer. Head and neck squamous cell carcinoma (HNSCC) is responsible for hundreds of thousands of deaths annually[51]. Thousands of patients with HNSCC have been treated using PDT[76]. Although surgery and radiotherapy are typically used to manage early stage HNSCC, PDT is appealing because the ability to spare most non-malignant tissues from treatment can enable better preservation of the delicate architecture of tumour-adjacent structures. Moreover, PDT of early stage disease does not interfere with future surgical or radiation treatments. Clinical studies of PDT in patients with HNSCC have focused on either curative-intent treatment of early stage disease or symptom palliation for those with advanced-stage disease, both of which are settings where the highly localized and minimally invasive nature of this modality offer advantages[77]. Given the various anatomical localizations of HNSCC, a multitude of different illumination strategies are possible, including surface or interstitial illumination (FIG. 1c) with or without imaging guidance[78].

PDT of patients with HNSCC was first described in 1984 (REF.[79]), for indications that included cancer of the tongue, nasopharynx, floor of mouth, soft palate, oropharynx, buccal mucosa, maxilla, larynx and basal cell nevus. Subsequent studies by various groups have confirmed the potential of PDT in the treatment of HNSCC. In general, HNSCC seems to be highly responsive to PDT, with Biel[80] reporting a CR in 255 of 276 patients with early stage laryngeal and oral cancers (92%). In another study[81], temoporfin PDT resulted in CRs in 97 (85%) of 114 patients with early stage oral squamous cell carcinoma who met the protocol requirements, which were maintained in 85% of responders at 1 year and in 77% at 2 years post-treatment. In a case series of 33 patients treated with porfimer sodium PDT between 1998 and 2016 at a single institution in Japan, 73% had a CR, and 97% had a complete or partial response. However, PDT is unlikely to supplant surgery as the primary standard-of-care treatment for early stage HNSCC in the absence of positive data from randomized controlled trials. Nevertheless, PDT might be useful for patients who have recurrence of HNSCC following surgery or radiation in whom surgery could result in considerable morbidity[82]. In a multicentre study,

19 (48.7%) of 39 patients with advanced-stage HNSCC had a CR to temoporfin PDT, demonstrating that this approach can achieve local control, with a median OS duration that was substantially longer for responders than for non-responders (37 months versus 7.4 months)[83]. In another multicentre study of temoporfin PDT in 128 patients with advanced-stage HNSCC, 38% of evaluable patients had an overall tumour response while 16% had a complete tumour response[84]. In patients with smaller tumours (<10 mm) that could be fully illuminated, the overall tumour response rate was 54%, with 61% of those patients having a considerable clinical quality-of-life benefit[84]. The median OS duration was 337 days for responders and 216 days for non-responders[84].

Indeed, temoporfin is approved by the EMA for selected patients with advanced-stage HNSCC for whom other treatments are not feasible (FIG. 2). A cost-analysis study from the UK has indicated that temoporfin PDT is a more cost-effective treatment option for patients with advanced-stage head and neck cancer than palliative chemotherapy or surgery[85]. Nevertheless, the small number of patients eligible for such therapy (that is, those who are not suitable candidates for other treatments) might limit interest in further developing PDT for HNSCC.

Skin cancers. Non-melanoma skin cancers or cutaneous precancerous lesions are important indications for PDT, with tens of millions of patients likely to have been treated worldwide to date. Topical PDT is non-invasive and is often used in the treatment of actinic keratosis, Bowen disease and basal cell carcinoma (BCC), generally with equivalent recurrence outcomes to those achieved with surgery but with superior cosmetic outcomes[86]. Actinic keratosis is a neoplastic condition of squamous cells that can progress to squamous cell carcinoma, Bowen disease is a form of squamous cell carcinoma in situ[87], and BCC is the most common form of skin cancer and indeed the most common human cancer. The topical photosensitizer ALA and its structural derivatives methyl aminolevulinate (MAL) and hexyl aminolevulinate (HAL) are small molecules that do not provide direct photosensitization; however, they are precursors of porphyrin that are converted to protoporphyrin IX (PPIX) via the haem synthesis pathway. PPIX that subsequently accumulates in cells serves as an endogenously produced photosensitizer to blue or red light applied to the target skin fields after a suitable interval. PPIX tends to accumulate at higher levels in malignant cells owing to mechanisms such as enhanced uptake and reduced ferrochelatase activity relative to that of non-malignant cells[88], which enables field treatment of large skin areas containing both non-malignant and malignant tissues with limited toxicity. However, such topical application approaches are only suitable for highly superficial neoplastic lesions.

The use of porphyrin precursors for topical PDT in clinical oncology was pioneered by Kennedy et al.[89], who, in 1990, reported that topical application of an ALA solution to actinic keratosis or superficial BCC lesions induced PPIX photosensitization: a 90% CR rate was observed in 80 treated BCC lesions. In a pilot dose-ranging study involving 40 patients, actinic keratosis lesions on the face or scalp responded better than on the trunk (total clearing of lesions in 91% versus 45% of patients)[90]. Subsequently, a proprietary single-use applicator system for topical delivery of a 20% ALA solution and a 417 nm blue light source was developed and was FDA approved in 1999 for the treatment of non-hyperkeratotic actinic keratosis of the face or scalp (FIG. 2) and is also approved in Korea, Mexico, Brazil, Argentina, Chile and Colombia[91]. Typical treatment parameters are ~17 min of irradiation at 10 J/cm^2, with the light treatment being applied 14–18 hours after topical application of ALA. Although this PDT platform is only approved for the treatment of actinic keratosis, it is also commonly used to treat BCC. A gel formulation of 10% ALA has also been developed and was approved by the EMA in 2011 for the treatment of actinic keratosis of the face and scalp. In 2016, the FDA also approved this formulation in combination with a red light (635 nm) LED lamp for the treatment of actinic keratosis of the face and scalp (FIG. 2). MAL, the methyl ester of ALA, is a more hydrophobic compound and can therefore more efficiently penetrate cells[92]. MAL has been developed as a 16% MAL topical cream in combination with a 570–670 nm wavelength red light lamp. This combination was approved by the EMA in 2001 for the treatment of actinic keratosis of the face and scalp and for the treatment of BCC as well as by the FDA in 2004 for the treatment of actinic keratosis (FIG. 2). These three topical formulations of ALA and MAL have been tested for several indications in clinical studies.

In a comparative trial[93], 16 patients with extensive actinic keratosis of the scalp were treated with 20% ALA cream on one side of the scalp and with MAL cream on the other. PDT with either formulation was shown to be effective, with mean reductions in actinic keratosis counts from baseline of 6.2 and 5.6, respectively; however, ALA PDT was reported to be more painful than MAL PDT[93]. In a multicentre, randomized, observer-blinded trial involving 600 patients with 4–8 moderate actinic keratosis lesions of the face and/or scalp, PDT with the 10% gel formulation of ALA induced a superior complete clearance rate compared with PDT using MAL cream (78.2% versus 64.2%; $P < 0.05$)[94].

In 2001, a phase III trial in 88 patients revealed that ALA PDT for BCC has a similar efficacy to cryosurgery (12-month histopathological and clinical recurrence rates of 25% and 5%, respectively, versus 15% and 13%), but with fewer AEs (including leakage of treated lesions, oedema, changes in skin pigmentation and scarring), shorter healing times and superior cosmetic outcomes[95]. In a multicentre randomized controlled trial involving 196 patients with superficial BCCs, MAL PDT resulted in efficacy outcomes comparable to those of surgery (CR rate at 3 months of 92.2% versus 99.2%; 12-month recurrence rate of 9.3% versus 0%) but with better cosmetic outcomes (deemed excellent or good in 94.1% versus 59.8%)[96]. In another multicentre randomized trial, MAL was shown to be an effective treatment option for patients with nodular BCC, with CRs in 48 (91%) of 53 patients compared with CRs in 51 (98%) of 52 patients treated with surgery; despite a higher recurrence rate

compared with surgery (17% versus 4% at 12 months), MAL PDT provided better cosmetic outcomes according to both patients and investigator evaluation[97]. In 2018, a phase III trial including 281 patients revealed that MAL cream provides similar results to 10% ALA gel in PDT for BCC; with multiple treatments, CRs were observed in >90% of patients with both formulations[98]. A meta-analysis of several randomized controlled trials has indicated that MAL PDT is inferior to surgery, but provided better cosmetic outcomes, and is not superior to ALA PDT in the treatment of BCC[99].

One interesting development in topical PDT is the use of daylight for excitation of the photosensitizer. With this approach, shortly following topical application of the formulation, instead of light irradiation at the clinic, patients spend time outside exposed to natural daylight. The photoactivation mechanism does not require ultraviolet light, thus patients can wear sunscreen for the protection of non-malignant skin. BCCs have been shown to respond to topical MAL in patients randomized to daylight exposure for 1.5 hours or 2.5 hours, with both durations resulting in a mean lesion response rate of ~75%[100]. Actinic keratosis is also responsive to daylight PDT with MAL or ALA[101]. Together, these studies reveal that daylight PDT is a nearly pain-free treatment, and guideline recommendations relating to the use of this approach in Europe[86] and in Australia[102] have been published. Daylight PDT remains an active area of research and has been granted EMA regulatory approval for the treatment of actinic keratosis (FIG. 2).

Emerging indications. PDT has been tested clinically for dozens of other cancer indications, including breast cancer[103], cholangiocarcinoma[104,105], pancreatic cancer[106,107] and gynaecological cancers[108]. Other types of skin cancer manifestations beyond those discussed above, such as melanoma[109] and cutaneous T cell lymphoma (with a phase III trial of hypericin PDT ongoing: NCT02448381), are also prominent targets. In addition, bladder cancer, brain cancer and prostate cancer have been targets of PDT for decades, and recent developments have generated new potential for PDT in these diseases.

Bladder cancer was the first indication for which porfimer sodium was approved (by Health Canada in 1993 for the treatment of recurrent superficial papillary bladder cancer[110]); however, AEs such as bladder contracture and fibrosis have limited the application of PDT in this setting[111]. Moreover, a phase III trial revealed that a single application of porfimer sodium PDT was not superior to the current standard of care of Bacillus Calmette–Guérin instillations for patients with non-muscle-invasive bladder cancer[112]. Nevertheless, the development of other photosensitizers, including ALA[113] or HAL[114] as instillation formulations, has renewed interest in PDT for bladder cancer. In clinical studies, the use of HAL for photodiagnosis using blue light illumination has been shown to improve the diagnostic accuracy of standard cystoscopy for bladder cancer[115]. This diagnostic approach was approved in Sweden in 2004, across Europe in 2006 and by the FDA in 2010 (FIG. 2). Another photosensitizer, TLD-1433, which is the first ruthenium-based photosensitizer to enter human clinical PDT trials[111], is currently being evaluated in a phase II trial for the treatment of non-muscle-invasive bladder cancer via intravesical infusion (NCT03945162).

Brain cancer is another indication for which PDT is receiving renewed interest[116]. In a report of PDT for newly diagnosed high-grade gliomas in 136 patients between 1986 and 2000, the median OS from initial diagnosis was 76.5 months for those with anaplastic astrocytoma and 14.3 months for those with glioblastoma (compared with 8 months without PDT in a historical control group)[117]. This PDT approach involves light irradiation of the surgical bed following surgical resection of the tumour in order to eradicate any residual tumour cells, with porfimer sodium, temoporfin, talaporfin or ALA having been explored as photosensitizers in this context[118]. ALA in particular has generated interest for PDT of high-grade gliomas[119], perhaps in part owing to the utility of ALA in fluorescence-guided resection (FGR), in which brain tumours can be distinguished from background tissue during surgery. In 2006, a randomized control trial involving 322 patients revealed that complete resection of contrast-enhancing tumours was achieved in 65% of patients with FGR following ingestion of ALA, but in just 36% of patients without FGR[120]. Accordingly, patients who underwent FGR had a higher 6-month progression-free survival (PFS; 41% versus 21%)[120]. In a trial of 59 patients with glioblastoma, the presence of strong ALA fluorescence showed a strong positive predictive value of 97.4% for correctly identifying tumour tissue in 211 biopsy samples[121]. Data from a randomized control trial in 27 patients with glioblastoma showed that administration of porfimer sodium intravenously and of ALA orally followed by FGR and repetitive PDT, with postoperative illumination of the resection cavity achieved via a balloon catheter, provides PFS and OS advantages without added risk to patients. The mean PFS and OS durations were 8.6 months and 52.8 weeks, respectively, versus 4.8 months and 24.6 weeks without ALA-based FGR and PDT[122]. Oral ALA alone has been used to induce PPIX fluorescence for PDT of unresectable glioblastomas via direct irradiation with interstitial light fibres, with three (60%) of five patients having strong PPIX fluorescence and disease stabilization lasting >29 months (those with no or low PPIX concentrations died within 9 months)[123]. In 2017, the FDA approved oral ALA for FGR of suspected high-grade gliomas (FIG. 2). Application of PDT together with FGR of brain tumours warrants exploration in larger-cohort clinical trials[124].

Prostate cancer is the second most common cancer in men, and debate continues regarding optimal treatment of organ-confined disease[125]. Several local treatment options are available, including radical prostatectomy and external beam radiotherapy as well as brachytherapy and cryotherapy, with the latter two approaches attracting attention owing to a potentially reduced risk of AEs[126]. PDT using various photosensitizers has also been tested in the clinic for the focal ablation of prostate tumours[127]. In 14 men with recurrent prostate cancer, temoporfin PDT with light applied using optical fibres inserted percutaneously through

perineal needles under imaging guidance resulted in necrosis in up to 91% of the prostate cross-section[128]. Serum prostate-specific antigen levels decreased in nine patients (64.3%), and five patients (35.7%) had no viable tumour detected in post-treatment biopsy samples[128]. With more precise light dosimetry, complete ablation of the glandular tissue within the prostate might be possible using this approach, with few complications (some stress incontinence and decreased sexual potency was observed in the aforementioned study[128]). Progress has also been made in the treatment of early stage prostate cancer with vascular-targeted PDT using water-soluble, palladium-chelated padeliporfin. Unlike with other photosensitizers, light is applied immediately after systemic administration of padeliporfin. In 2017, the results of a phase III trial in 413 men with low-risk prostate cancer demonstrated that 28% of patients treated with padeliporfin PDT had disease progression at 24 months compared with 58% in an active surveillance group[129]. The most common serious AE in the vascular-targeted PDT group was retention of urine, an effect that resolved within 2 months. Since 2018, padeliporfin has been approved by Mexico's health authority and the EMA for the local treatment of early stage prostate cancer (FIG. 2).

Progress of PTT towards the clinic

The clinical development of PTT has had a different trajectory compared with that of PDT. Whereas PDT is largely a photochemical process that relies on light interaction with a photosensitizer, PTT is simply enhanced by photothermal contrast from exogenous agents (FIG. 1b), and thermal ablation can also be achieved through excitation of endogenous chromophores within human tissues. Thus, whereas clinical PDT has been predicated on the use, pharmacokinetics, biodistribution and photochemistry of photosensitizers, clinical laser-thermal therapies have been mostly developed as device-only approaches. Avoiding the use of a PTT contrast agent greatly simplifies regulatory strategies and reduces development costs. Indeed, a disconnect between the focus of preclinical and clinical PTT studies is evident, with widespread preclinical research concentrated on the characterization of new photothermal contrast agents, whereas clinical studies are typically centred on the development of integrated laser device ablation systems that do not rely on exogenous contrast. This disparity might reflect the fact that contrast-dependent PTT tumour ablation can readily be demonstrated in preclinical tumour models, enabling rapid, reproducible and less resource-intensive testing of a wide variety of novel compounds and materials. As discussed further below, phase I trials involving gold nanoshells have shown that PTT agents do hold potential, but their clinical development status is considerably behind that of PDT and contrast-free laser thermal therapy.

Laser devices alone can be used to administer PTT for cancer. For example, Nd:YAG and other lasers can be used for endoscopic irradiation of obstructing endobronchial cancers and thus for their ablation through photocoagulation[130]. Laser interstitial thermal therapy (LITT) generally involves placement of laser fibres into tumours and has been explored for various cancer indications. With these approaches, the positioning of the laser fibres provides the only means of selectivity for the target tissue, and thus LITT is in direct competition with other interventional oncology ablation modalities such as radiofrequency ablation and microwave ablation.

LITT has long been used in several solid tumour indications, including prostate[131] and liver tumours[132]. In 2004, results of the treatment of 603 patients with liver metastases from colorectal carcinoma (<5 cm in diameter) with LITT under MRI guidance were reported[133]. The rate of local recurrence 6 months post-LITT was approximately 2% for tumours <4 cm in diameter and 4.4% for larger tumours[133]. In this study, a Nd:YAG laser with 1,064 nm output wavelength was used to generate photothermal energy. The same group had previously reported results of a clinical study involving MRI-guided LITT in 899 patients with malignant liver tumours, which yielded an acceptably low rate of major complications such as pleural effusion, hepatic abscess, bile duct injury, segmental infarction and haemorrhage (all of which occurred in <1% of patients)[134]. Another study of the use of percutaneous LITT in 500 patients with hepatocellular carcinoma revealed this approach to be safe and effective: 15 (1.5%) of 1,004 LITT sessions resulted in major complications (which were associated with higher laser energies and high-risk tumour locations), and the ablation efficacy was 60% overall and 81% for tumours <3 cm in diameter[135].

Several LITT devices have successfully entered the market or are in late-phase clinical testing, with MRI-guided LITT for brain tumours as a major focus. Two devices were approved by the FDA in the late 2000s for the stereotactic laser ablation of high-grade gliomas: the Visualase Thermal Therapy System and the Neuroblate Laser Ablation System[136,137]. These two systems share similar hardware features, including cooled fibres, as well as treatment protocols involving MRI guidance for imaging analysis and system control. However, the Neuroblate system uses a 12 W, pulsed 1,064 nm laser, whereas Visualase uses a 15 W, 980 nm laser[138]. With both systems, following treatment planning, holes are drilled in the skull and a laser catheter, either spherically diffusing or directional, is inserted under MRI guidance. Laser light is then used to achieve local heating with local temperature response being measured by thermocouple or magnetic resonance thermometry. Although several small studies of these platforms have been conducted, no prospective randomized or case–control trials have demonstrated the efficacy of LITT in patients with gliomas[139]. The Novilase system provides another approach to LITT designed for the ablation of mammary tumours and is currently being tested in phase III trials for the treatment of fibroadenoma (a type of benign breast tumour; NCT00807924). In a phase II trial of laser treatment of invasive ductal breast carcinomas prior to tumour resection, 51 (83.6%) of 61 patients had complete tumour ablation on pathology analysis[140].

Contrast-enhanced PTT can offer improvements over conventional LITT, including better selectivity for the target tissue. Furthermore, the use of a photothermal contrast agent can enable the use of lower-power

lasers and thus simplify device design, which is complicated by the requirement for high laser power and the resultant need for integrated fibre cooling systems. To date, however, clinical studies of contrast-enhanced PTT have been limited to a few early phase pilot trials, as discussed below.

The use of gold nanoshells and related light-absorbing nanomaterials as PTT contrast agents has received much research interest, although most studies have been limited to preclinical models[141]. In 2019, results of a phase I trial demonstrated the feasibility of an approach involving sterile nanoshells with a silica core and gold shell for focal PTT ablation of prostate tumours[142]; 16 patients received a single infusion of gold nanoshells and subsequently underwent interstitial laser placement of up to 21 optical fibres (up to 1.8 cm in length) within the tumour under MRI and ultrasonography guidance, followed by laser treatment with 6.5 W of 808 nm light. Tumours were successfully ablated in 94% of patients, with no serious complications and no marked change in symptom or sexual health scores[142]. Beyond prostate cancer, pilot studies of this PTT platform have also been conducted in patients with head and neck cancer (NCT00848042).

Indocyanine green, an NIR dye that is approved by the FDA for use in fluorescence angiography, was shown >20 years ago to be an effective contrast agent for PTT with a 805 nm laser in preclinical tumour models[143]. This agent has also been examined as a photosensitizing agent for PDT, although its singlet oxygen generation capacity is much lower than that of conventional photosensitizers[144]. The track record of human use of this dye should facilitate the clinical translation of new phototherapy approaches using this agent. Li et al.[145] reported the clinical translation of an indocyanine green PTT approach for laser immunotherapy to local tumour ablation in patients with treatment-refractory advanced-stage metastatic breast cancer. Superficial tumours in ten patients were locally injected with an indocyanine green formulation and the immunoadjuvant glycated chitosan, followed by irradiation of the lesion with an 805 nm laser at a power of 1 W/cm^2. AEs were limited to local thermal injury and/or immune reactions; no serious AEs occurred. The objective response rate of the target lesions was 62.5%[145].

Challenges and bioengineering solutions

As outlined above, various approaches to PTT and PDT have been tested — and in some cases have made inroads — in certain oncology indications; however, clinical adoption has not reached its full potential for reasons that probably relate to variability in patient outcomes as well as to complexity in applying a laser-mediated drug–device combination in the clinical setting. To compete favourably with surgery or device-only ablation modalities and justify usage, phototherapies must provide substantial benefits in terms of clinical outcomes or ease of use. Although the current generation of clinically used photosensitizers provides some level of specificity for malignant tissues, efforts to develop next-generation agents aim to improve on this tumour specificity. Generally, the limited selectivity of PTT and PDT agents for tumour tissues over the surrounding non-malignant tissues necessitates the use of high doses to ensure a therapeutic effect. Consequently, the accumulation of the photosensitizer in tumour-adjacent tissues and organs and stray light extending beyond the treated tumour volumes can result in collateral damage. In addition, the limited penetration of light through biological tissues means that PTT and PDT are typically ineffective for deep-seated tumours. Moreover, the efficacy of PDT against hypoxic tumours is poor because the therapeutic effects are oxygen dependent. Furthermore, potential skin toxicities caused by the undesired excitation of residual photosensitizers requires patients to stay in the dark for a substantial period of time after PDT. In the following sections, we discuss efforts to overcome these drawbacks.

Targeting strategies

Targeting strategies to improve the delivery of photothermal and photodynamic agents to tumour tissues have the potential to simultaneously enhance the selectivity and efficacy of PTT and PDT and have received much attention. Both passive targeting and active targeting are currently being explored. Passive targeting can be achieved by adjusting the size and surface chemistry of nanoparticle (or macromolecule) agents to promote their selective accumulation in tumours through the enhanced permeability and retention (EPR) effect[146]. The EPR effect is generally attributed to the rapid growth of cancer cells, which consume local nutrients at a high rate and induce the dysregulated generation of imperfect blood vessels. Leaky pores in these new blood vessels can enhance the penetration of circulating nanoparticles into the tumour environment, whereas the penetration in non-malignant tissues is restricted by the intact vasculature barrier. In addition, nanoparticles tend to be selectively retained in tumour tissues owing to the impaired lymphatic drainage system therein. To achieve the passive targeting effect, nanoparticles are generally required to have sizes of 10–200 nm (REF.[147]). Besides size, other inherent characteristics of nanoparticles, such as shape, electrical charge, hydrophilicity and circulation time in blood, affect the efficiency of passive targeting of tumours[148]. The effectiveness of EPR-based targeting in vivo has been demonstrated in preclinical tumour models, although this approach has several drawbacks[146]. In some early stage tumours, the EPR effect might be limited owing to their small size and more regular vasculature. Moreover, the malformation of vessel fenestrations is typically heterogeneous within a tumour mass such that EPR-mediated targeting would not be homogeneous throughout[149]. Crucially, the extent and relevance of the EPR effect — or even if it occurs at all — in human tumours, rather than in fast-growing tumours in murine models, are questionable[150].

Active targeting to improve tumour selectivity typically involves the use of high-affinity ligands that engage specific surface molecules predominately expressed by cancer cells or tumour epithelial cells. Various ligands have been explored for the active targeting of PTT and PDT agents, including peptides (such as arginine–glycine–aspartate peptide and epidermal growth

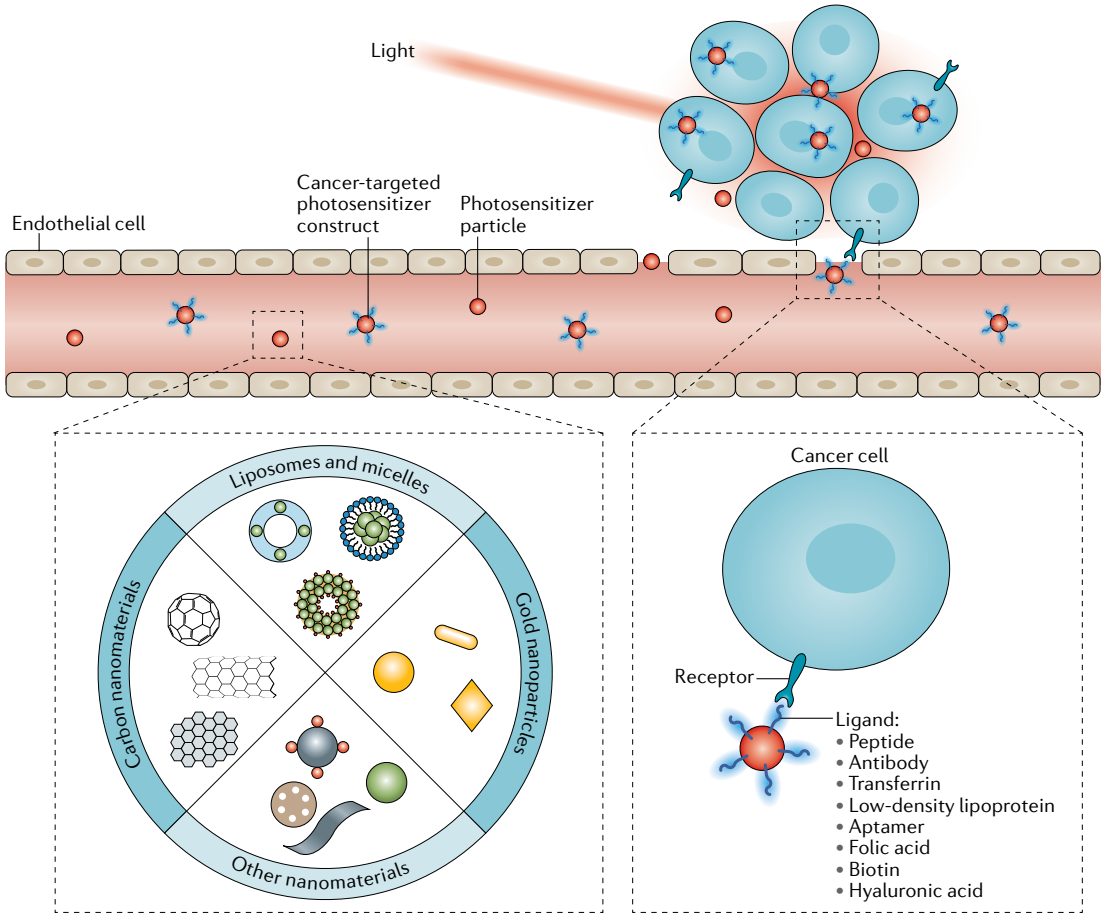

Fig. 3 | **The use of nanoparticles and ligands to target cancers through PTT and PDT.** Various nanoparticle constructs, including liposomes, micelles, carbon nanomaterials and gold nanoparticles, are being explored as vehicles for the delivery of photosensitizers used for photodynamic therapy (PDT) or photothermal therapy (PTT) selectively to cancers. Untargeted nanoparticles might accumulate selectively in tumours owing to the enhanced permeability and retention effect, whereas ligand-grafted nanoparticles enable active tumour targeting through binding to specific receptors overexpressed by cancer cells.

factor)[151,152], proteins (for example, transferrin and antibodies)[153,154], aptamers[155], vitamins (such as folic acid and biotin)[156,157] and carbohydrates[158] (FIG. 3). Monoclonal antibodies, which have exquisite targeting specificity and are used extensively as human therapeutics, have been explored as photosensitizer carriers for PDT. This approach is referred to as photoimmunotherapy and was pioneered by Levy et al. in 1983 (REF.[159]) and has subsequently been developed by many groups[160]. The first-in-human study of photoimmunotherapy was reported by Schmidt et al.[161] in 1992, with PDT with an antibody-targeted phthalocyanine demonstrated to induce tumour cell killing in three patients with ovarian cancer. An IR-700 phthalocyanine-conjugated anti-EGFR monoclonal antibody (ASP-1929) has been developed[162] and has entered phase III testing in patients with recurrent HNSCC (NCT037695060).

Besides passive and active targeting, physical forces (such as magnetic or electric fields) can also be used to enhance the targeting of PTT and PDT agents to tumours. Magnetic nanoparticles (for example, based on superparamagnetic Fe_3O_4) carrying photosensitive agents in the blood can be redirected to and accumulated in tumour tissues with an applied external magnetic field, thereby improving the selectivity and efficiency of PTT and PDT. Magnetic field-directed PTT and PDT have been applied successfully in preclinical models[163–165].

The aforementioned strategies can facilitate the accumulation of PTT and PDT agents in the extracellular matrix of tumour tissues and/or enable selective binding to the surface of cancer cells. In addition, subcellular targeting might affect therapeutic outcomes, particularly with PDT. Singlet oxygen has a short lifetime (≈200 ns in cells) and a limited diffusion distance (≈50 nm)[166] and thus causes damage only in the immediate vicinity of the photosensitizer molecule involved in its generation. Thus, the localization of photosensitizers to subcellular organelles, such as lysosomes, mitochondria and nuclei, might be favourable in order to enhance the cytotoxic activity and thus efficacy of PDT[167,168]. Certain chemical modifications, such as triphenylphosphonium derivatives (which preferentially insert into the inner mitochondrial membrane) and nucleus-targeted peptides, can actively target photosensitizers to localize in mitochondria and nuclei, respectively[169–171].

Aptamers
Oligonucleotides or peptides that bind to a specific target molecule.

Photochemical internalization

Directing active pharmacological compounds not only to their target tissues but also to their typically intracellular sites of action is a key challenge for drug delivery. The latter is particularly challenging with large or hydrophilic therapeutic cargos, which tend to be retained or degraded within subcellular endosomes, limiting their entry into the cytosol or target organelle. However, this effect can also be exploited through photochemical internalization, which is a drug-delivery method predicated on the use of PDT to selectively disrupt those endocytic vesicles, thereby releasing active cargo molecules from endosomes and lysosomes into the cytosol within the illuminated cells and tissues[172]. For photochemical internalization, photosensitizers with an inherent affinity to localize to endocytic vesicles, such as tetraphenyl chlorin disulfonate ($TPCS_{2a}$, also known as fimaporfin), are used to trigger the release of co-administered drugs that are also sequestered into endosomes[173]. This approach has been demonstrated in preclinical models for a range of cargos, including proteins, nucleic acids and chemotherapy drugs such as bleomycin[174]. The photochemical internalization of bleomycin, using fimaporfin as the photosensitizer, has been demonstrated to be safe and tolerable in a phase I trial involving 22 patients with solid tumours[175]. The most common grade ≥3 AE was treatment-site pain (in nine patients), and skin sensitivity was the predominant dose-limited toxicity[175]. This method of drug delivery has also been proposed for cancer vaccines, and this approach has been shown to enhance the delivery and presentation of MHC class I antigens[176].

Light replacement

The light source acts as an external 'on/off' switch controlling PTT and PDT. To successfully implement PTT and PDT in vivo, the light source must have two characteristics: first, a suitable spectral range, coinciding with the peak absorption wavelength of the administered photosensitive agent; second, a sufficient tissue-penetration depth with minimal power loss. Most photosensitizers used for PDT have absorption maxima in the visible range. However, many endogenous chromophores (for example, cytochromes) in biological tissues can also absorb visible light. In addition, the heterogeneous structure of biological tissues causes scattering such that the light spreads and loses directionality[177]. Typically, long-wavelength red light in the visible spectrum has a tissue-penetration depth of only several millimetres, which makes PDT challenging for deep-seated tumours and necessitates approaches such as the interstitial delivery of light[178]. Longer-wavelength NIR light minimizes the degree of tissue scatter compared with that of visible light and can have penetration depths exceeding 1 cm (REF.[179]). Photosensitizers can be excited using light with longer NIR wavelengths if they are sensitive to two-photon excitation[180] or if they can be combined with upconverting nanoparticles[181]. Most current PTT agents are excited by light in the first NIR range (NIR-I; 700–1,000 nm) but methodological development towards illumination in the NIR-II range (1,000–1,350 nm) could further improve treatment outcomes because NIR-II light is less affected than NIR-I by scattering in tissues[182,183]. Other than NIR light, X-ray radiation is also a promising energy source to enable effective PDT and PTT for deep-seated tumours[184,185]. These systems require the use of scintillators that generate light upon X-ray excitation, which in turn can activate nearby photosensitizers. Besides external excitation sources, PDT agents can also be designed to be excited by photons generated by enzyme-mediated bioluminescence approaches, thereby overcoming depth limitations[186]. The development of NIR light-emitting nanoparticles with very long luminescence lifetimes, thereby enabling persistent excitation of photosensitizers for PDT, might provide another means to avoiding the use of external light irradiation[187,188].

Oxygen replenishment

The fast growth of cancer cells and an insufficient blood supply lead to a hypoxic microenvironment in tumours[189], which reduces the antitumour efficacy of oxygen-dependent PDT. Several strategies have been proposed to overcome this problem. These strategies can generally be divided into three categories based on the mechanism of action: (1) oxygen-replenishing strategies that can directly (by using a carrier to deliver oxygen into tumours) or indirectly (by regulating hypoxia-inducer factor activity or slowing down respiration) increase the oxygen concentration in tumour tissues before and during PDT[190,191]; (2) strategies using new PDT paradigms that are less dependent on high oxygen levels such as type I PDT or fractional PDT (which involves intermittent light irradiation and might reduce oxygen consumption)[192,193]; and (3) strategies involving the combination of PDT with other oxygen-independent or hypoxia-activated therapeutic modalities[194,195].

Activatable photosensitizers

With current PDT approaches, the photosensitizers used are usually 'always on'. Thus, patients must keep away from sunlight for extended periods of time after treatment until the photosensitizer is eliminated from the body in order to avoid photosensitivity and phototoxicity in non-malignant tissues. For example, after treatment with 'always on' photosensitizers, the eyes are vulnerable to light, and skin tends to get easily sunburned, swollen and blistered[196,197]. Over the past decade, activatable photosensitizers with the potential to overcome this shortcoming of PDT have been developed[198–201]. Ideally, activatable photosensitizers should remain in an inactivated, 'off' state unless activated to the 'on' state by tumour-associated factors (FIG. 4), such as cathepsin B, matrix metalloproteinases, glutathione, hydrogen peroxide, slightly acidic conditions or hypoxia, present either in the extracellular matrix or intracellularly within tumours. This switch often involves cleavage of an intramolecular linker connecting the photosensitizer to a quenching moiety, thereby increasing the singlet oxygen yield. Thus, activatable photosensitizers extend beyond the typical two-layered selectivity intrinsic to PDT (that is, selective photosensitizer accumulation and focal laser irradiation) owing to the additional requirement of tumour-associated stimuli, which can ensure

Absorption maxima
The specific wavelength of light that chromophores absorb most intensely.

Two-photon excitation
Simultaneous excitation by two photons at double the excitation wavelength.

Upconverting nanoparticles
Particles that convert near-infrared excitation light into visible and ultraviolet emission light.

Quenching moiety
A molecule that attenuates the fluorescence or singlet oxygen generation of a fluorophore or photosensitizer.

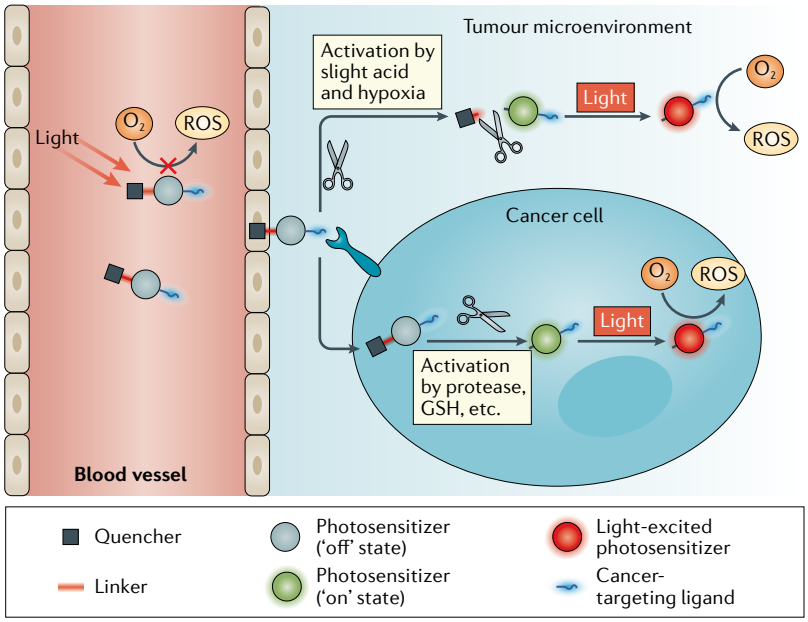

Fig. 4 | **Activatable photosensitizers for cancer-specific PDT.** In the blood, activatable photosensitizers remain in a passive ('off') state, even under light irradiation. After delivery into tumour tissues, the activatable photosensitizers can become activated ('on' state) by cancer-associated stimuli, such as the slightly acidic and/or hypoxic conditions in the tumour microenvironment, proteases overexpressed by tumour cells or intracellular glutathione (GSH), and subsequently, upon absorption of photons, promote the generation of reactive oxygen species (ROS) that result in damage to tumour tissues. PDT, photodynamic therapy.

a highly specific, localized PDT response. Given such heightened control, activatable photosensitizer-based PDT provides the potential for minimizing AEs and has become a guiding strategy for researchers pursuing precision treatments.

Combination with other therapies

Eradicating solid tumours completely by PTT or PDT alone (particularly following a single course of treatment) can be difficult owing to the inherent drawbacks of these therapies. The combination of PTT and/or PDT with other therapeutic modalities could provide opportunities to exploit the advantages and offset the disadvantages of each therapeutic modality (FIG. 5), leading to additive or even synergistic therapeutic effects. Nanotechnology might play a prominent role in combination therapy approaches because nanoplatforms present a vehicle for the integration of various agents associated with different therapeutic paradigms. However, several proposed combination partners for phototherapy, such as chemotherapy or immunotherapy, are already well-established, standard-of-care treatments; therefore, initial clinical studies are likely to involve the combination of phototherapy with currently approved treatments. Cooperative interactions between different therapies could potentially increase the antitumour efficacy at lower doses of photosensitive agents or lower-power light irradiation, thus minimizing potential toxicity to non-malignant tissues. In addition, multimodal therapies incorporating PTT and PDT are promising for confronting multidrug resistance (MDR) and hypoxia-related resistance to cancer therapy.

Dual-modal PTT and PDT

The combination of PTT and PDT has potential synergistic effects: the heating effect of PTT can enhance the intracellular delivery of the photosensitizer as well as improve local blood flow and increase the oxygen concentration in tumour tissues, thus resulting in a higher PDT efficacy[202,203]. Additionally, ROS generated during PDT can disrupt heat-shock proteins, thereby negating their protective effects in tumour cells during PTT[204]. However, due to the commonly mismatched absorption spectra of photothermal agents and photodynamic agents, combined PTT and PDT require sequential tumour irradiation using two different lasers, which prolongs treatment times and complicates the treatment process. Alternatively, single laser-triggered simultaneous PTT and PDT, based on the use of a photothermal agent coupled with a photodynamic agent or a dual-modal photothermal and photodynamic agent, has been reported[205,206]. This approach to combining PDT and PTT simplifies the treatment process and has been associated with improved therapeutic outcomes relative to single modality treatment in preclinical models, although the requirement for relatively high-power laser irradiation (≥1 W/cm^2) of long duration (>5 min) to trigger synergistic PTT and PDT effects, or even single-modality PTT activity, raises concerns. Therefore, simultaneous PTT and PDT approaches that use a single low-power NIR laser for short durations of irradiation need to be developed in order to simplify treatment and avoid laser-related toxicities[207].

Combined PDT or PTT and chemotherapy

The combination of photosensitive agents and chemotherapeutic drugs might induce synergistic therapeutic effects: chemotherapeutics can address the limitation of light penetration in phototherapy and might also enhance the sensitivity of cancer cells to hyperthermia or ROS, while the broad-spectrum activity and lack of resistance to phototherapy provide activity against drug-resistant cancer cells[208,209]. MDR mechanisms involving cell membrane efflux pumps are the predominant cause of treatment failure with chemotherapy[210]. Various drug-delivery systems have been developed to improve the accumulation of chemotherapeutic drugs into the cytoplasm or nucleus by avoiding or decreasing drug efflux[211–213]. The combination of chemotherapy and PDT might also enhance treatment efficacy owing to inhibition of drug-efflux P-glycoprotein pumps in MDR cells resulting from ROS generation by the photosensitizer[214]. Besides MDR, tumour hypoxia also reduces the therapeutic effects of chemotherapy[215]; however, the combination of chemotherapy and PTT might produce synergistic activity against tumour hypoxia via the aforementioned effects on blood flow and oxygen saturation.

Combined PDT or PTT and immunotherapy

The induction of a systemic anticancer immune response through localized photoablation of a given tumour would be highly beneficial to potentially eradicate overt or occult disseminated disease. PTT and PDT have been reported to cause immunogenic cell death (ICD)[36,216],

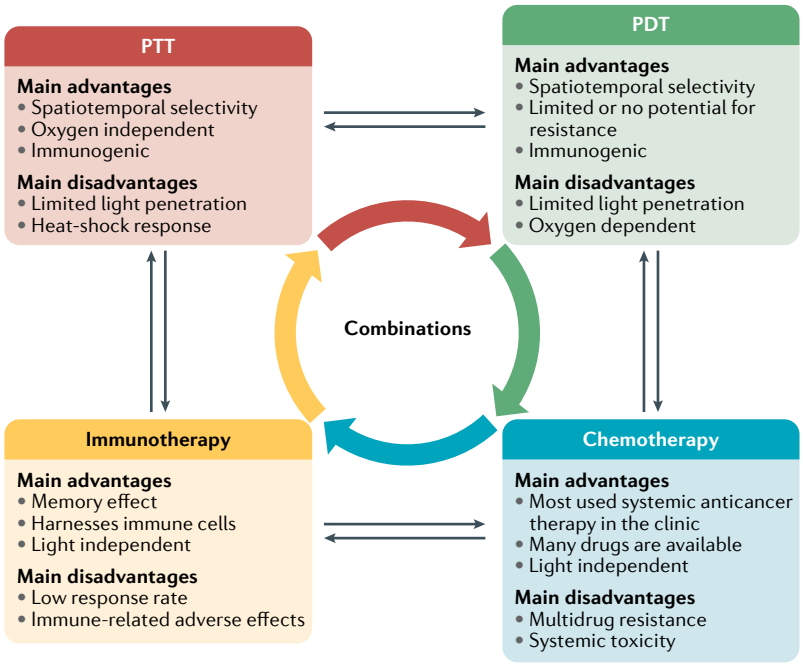

Fig. 5 | **Potential combinations of PDT and/or PTT with other cancer therapies.** Photothermal therapy (PTT) and photodynamic therapy (PDT) could potentially be combined with each other or with different therapeutic modalities, particularly immunotherapy and/or chemotherapy, in order to exploit the advantages of each therapeutic modality and offset their disadvantages. For example, the combination of PDT or PTT with immunotherapy could be synergistic owing to the immunogenic nature of the former, which might enhance antitumour immune response, while immunotherapy might enhance 'abscopal' responses in lesions inaccessible to PDT or PTT.

which results in the release of damage-associated molecular patterns and can consequently increase the immunogenicity of tumours. Accordingly, researchers have initiated efforts to exploit ICD arising from PTT and PDT to augment the efficacy of immunotherapy[36]. Generally, PTT and PDT can enhance immunotherapeutic responses through the following four mechanisms: (1) ICD induced by PTT and PDT permits effective destruction of the treated tumour with contributions by local immune cells; (2) tumour-specific antigens released as a result of ICD can act as an in situ vaccine[217]; (3) damage-associated molecular patterns boost the typically weak immunogenicity of native tumour antigens[218]; and (4) pro-inflammatory cytokines are upregulated and promote the activation of the immune system. These effects can synergize with those of immunotherapies that either enhance the immunogenicity of the tumour, such as immunoadjuvants, or reduce immunosuppression in the tumour environment, such as immune-checkpoint inhibitors (for example, anti-PD-1, anti-PD-L1 and anti-CTLA4 antibodies), ultimately increasing tumour infiltration of cytotoxic $CD8^+$ T cells and effector memory T cells. Preclinical results have shown that immune-checkpoint inhibition can have dramatic anticancer effects when combined with PTT and molecular adjuvants[219]. Thus, the combination of PTT or PDT with immunotherapy has the potential to effectively eradicate the target tumour as well as any residual cancer cells and metastases and could also trigger immunological memory to prevent tumour recurrence and provide the possibility of cure. PDT has been combined with immune-checkpoint inhibitors in the clinical setting, with a sustained CR reported in a patients with HNSCC refractory to multiple prior therapies[220].

Conclusions

The past 30 years have witnessed the clinical introduction of PDT and PTT as approved or experimental treatment options for several solid neoplasms. Topical PDT has become a mainstream treatment option for patients with actinic keratosis or BCC, which establishes the long-term viability of PDT as a treatment modality. Despite demonstrated efficacy and regulatory approvals, PDT with systemically delivered photosensitizers seems to be an underused tumour ablation modality. The reasons for this limited uptake are uncertain but might pertain to inconsistency in clinical results, a lack of superior efficacy over other local ablation modalities or surgery, or the complexity of the treatment (which involves both a drug and device). Several medical devices that do not require contrast agents have been successfully developed for cancer PTT. Contrast-enhanced PTT is an emerging focus of research for which potential clinical utility remains to be established, and ongoing clinical trials (for example, of gold nanoshells for prostate cancer ablation: NCT04240639) point to further interest in this area.

As biomedical optics technologies continue to produce light sources with increased power as well as the capability for the use of multiple fibres and decreased size and costs, interest in phototherapies is expected to remain high. Indeed, phototherapies are actively being pursued for a broad range of indications. Furthermore, next-generation and nanoscale photosensitizing agents have produced impressive preclinical results, but with limited clinical translation to date. Ironically, the advanced targeting and activation features of these agents might lead to manufacturing complexities that impede their clinical translation. Nevertheless, antibody-targeted PDT, or photoimmunotherapy, is under investigation in large-cohort clinical trials and holds potential to move forward as a next-generation technology.

As preclinical interest in novel photosensitizers for PDT and PTT continues to increase, agents will continue to be developed in order to harness novel and innovative designs with improved capabilities for targeting, selectivity, activation or image guidance. Importantly, the efficacy, ease of use and competitiveness compared to established modalities should all be considered as key metrics in these development efforts. Beyond advances in the agents themselves, advances in light delivery and indication selection will also be crucial for successful clinical translation. In general, the photoablation of large and/or deep-seated tumours is an area of unmet clinical need that is rarely considered in preclinical studies. Light delivery using multiple interstitial fibres is a promising approach that warrants further attention. Considerable room exists for the clinical expansion of new PDT and PTT platforms with rational technological innovations and strategic improvements.

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