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Avenues for integrating photothermal therapy in cancer clinic

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Experimental cancer therapeutics are rapidly advancing, with novel approaches emerging to reduce global cancer burden. This review focuses on challenges hindering the clinical integration of photothermal therapy (PTT), despite its therapeutic potential. Key PTT considerations include photothermal agent (PTA), laser properties and strategies for better application, efficacy and precision. Common parameters for PTA evaluation demonstrate biocompatibility, biodistribution and efficacy assessments. However, for clinical emphasis, targeting efficiency and post-therapy fate determination of PTA, sophisticated engineering of photonic devices, precision assessments as well as pain mitigation are critical. Directed future endeavours, keeping these insights, may facilitate application of PTT as a viable cancer treatment in clinical settings.

According to the World Health Organization (WHO) report in 2022, approximately 20 million new cases of cancer and 9.7 million deaths were reported. The number of individuals estimated to have survived for only five years after diagnosis was 53.5 million. Looking ahead to 2050, the projected increase in the global cancer burden is substantial, with over 35 million new cases anticipated, representing a 77% rise from the estimated cases reported in 2022 (https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing–amidst-mounting-need-for-services). It is estimated that approximately one in nine men and one in twelve women will develop cancer during their lifetime. Clearly, the conventional standard of care treatment procedures, which primarily include surgical interventions, radiation therapy, and chemotherapy or a combination of these, are not enough to win the 'war against cancer'. Further, due to high risk of treatment-related toxicity, chance of invariable disease relapse and metastatic spread as well as compromised living experience post-therapy in many aggressive types or subtypes of cancers, global cancer burden status and healthcare cost are reaching to an alarming state. In this context, clinical practice must look for accommodating newer therapeutic approaches such as nanomedicine, immunotherapy and other novel experimental treatment approaches developed demonstrating exemplary precision and efficacy[1].

The application of heat for cancer treatment started in the 20th century[2]. The temperature-driven cellular ablation strategy induced by non-ionizing radiation was termed as 'hyperthermia'. Eventually, hyperthermia became a field of active research, where clinical trials combining hyperthermia with radiation or chemotherapy were attempted in various cancers, including breast, head and neck, and bladder cancers[3]. Among different modes of hyperthermic treatment, magnetic induction, focused ultrasound, and photonic laser-guided therapy procedures showed distinctive efficacy as an anti-cancer therapeutic strategy. In PTT, synthetic nanoscale photothermal agents (PTAs) convert incident light energy into a sharp increase of heat, and thereby causing tissue ablation[4] (Fig. 1). Upon near-infrared (NIR) irradiation on the target tissue area with accumulated PTAs, a localized hyperthermia triggers cell death due to irreversible protein denaturation and damage of the cancer cells. This same effect does not apply for the neighbouring tissue environment where either the PTA or the photonic exposure is absent[4,5]. Temperature-dependent modes of cell death post PTT report a higher percentage of cells undergoing necrosis upon temperature elevation > 49 °C while 46–49 °C induce apoptosis as the more relevant mode of cell death[6]. Moreover, the autophagic mode of cell death has also been popularly reported as a result of protein disruption, causing unfolded protein response (UPR) pathway upregulation and increased reactive oxygen species (ROS), causing DNA damage[7,8].

As this research field is growing, a good number of PTA materials are developed and tested for their therapeutic efficacy in preclinical model systems. PTT procedure using several such materials developed has proven to be minimally invasive, precise and relatively non-toxic in nature. As a new entity in the realm of cancer treatment approaches developed through research, prospective use of PTT to manage radiation- and chemo-resistant cancers was also demonstrated in a preclinical model[7]. The ability of PTT procedure to treat a primary tumour that cannot respond to standardized care procedures, indicates the merits and potential this procedure holds. For example, PTT can be less invasive than surgery for treating localized tumours, potentially reducing patient morbidity and recovery time. Importantly, this physical mode of treatment procedure represents a limited risk of developing resistance against the treatment procedure. Here, we take an account of the important validation steps from past preclinical and clinical studies, where promising PTAs were tested for solid tumour treatment.

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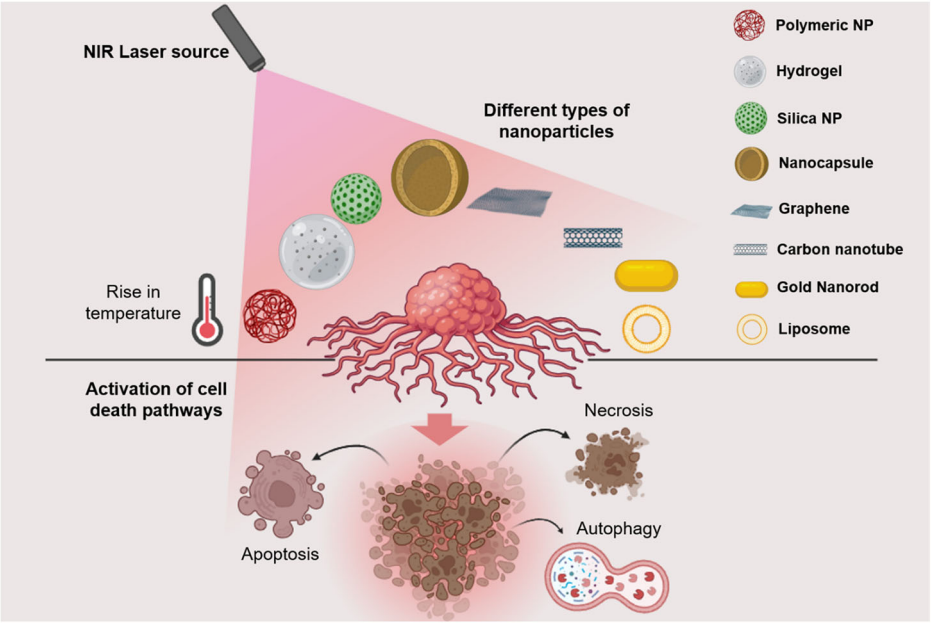

Fig. 1 | Principle of PTT. NIR laser irradiation on plasmonic nanoparticles leads to the generation of localised heat at the tumour site, leading to cell ablation primarily by necrotic, apoptotic, or autophagic processes.

Table 1 | Types of photothermal agents (PTAs) and their implications

Photothermal Agents	Examples	Advantages	Disadvantages
Organic dye compounds	Indocyanine green (ICG)[117,118], Prussian blue[119–122] IR dyes like BF_2[123,124], IR780, IR800, IR825, Porphysome[125]	• Excellent PCE • Thermostable • Used for photoacoustic imaging purpose	• Photobleaching • Instability • Solvent toxicity • Poor tumour targeting ability
Carbon nanomaterials	Carbon nanotubes[126–129],Graphene and graphene oxide[130,131]	• Excellent biocompatibility • Better bioavailability • Enhanced cargo-loading capacity	• Lower PCE • Poor biodegradability • Toxicity • Complex synthesis methods
Metal-based agents	Zinc-based gold nanocomposite[132,133], Copper-based NPs[132,134–136], Gold nanostructures[137–139], Plasmonic gold nanostars[139–142], Plasmonic gold semi-shells[143], SPIONS[144,145]	• Excellent PCE • Easier surface modification • Thermostable • Non-toxic • Enhanced specificity	• Stability concerns (potential for aggregation) • Immunotoxicity • Limited selectivity
Conjugate-based agents	Polypyrrole nanomaterials[146,147], Conjugated polymers[30,46,148], Carbon-silica nanocomposites[149], Gold-decorated melanin nanoparticles[118], Lanthanide ion-based up-conversion nanomaterial[150], Biomimetic gold nanoformulation[151]	• Enhanced PCE • Increased tumour targeting and accumulation • Multimodal imaging support • Versatile surface modifications	• Often complex synthesis and characterization procedures • Toxicity concerns • Limited thermostability

Applications of PTT as cancer therapeutics

A wide range of nano-sized materials or chemical moieties were tested as PTAs, which showed that the efficacy of a PTA is directly related to the optical property of the material. An ideal PTA should have high photothermal conversion efficiency (PCE), thermal stability, provision of suitable surface modification with proper peak tunability, and more importantly, effortless scale-up ability[9,10]. Further to enhance tumour targeting and reduce off-target effects, PTAs are often conjugated with targeting moieties on the material surface, such as antibodies, peptides, polymers etc. The point to be noted here is that such modifications may only help material's selectivity and improve bioavailability, but not intrinsic properties such as the photothermal conversion efficiency of the PTA itself. Table 1 summarizes different classes of PTAs synthesized along with their merits and demerits.

The development and application of a variety of plasmonic nanomaterials have been extensively studied, demonstrating their utility for PTT. For clinical use, it is crucial to evaluate for material toxicity, pharmacokinetics, survival benefits after treatment, treatment precision, as well as bystander effects using physiologically relevant preclinical models. Clinical trials involving larger animals like canines and felines have also been attempted, showing promising therapy efficacy in treated solid tumours, outlined in Table 2. However, beyond these attempts, clinical transition of various other PTAs with promising preclinical results have not moved towards translation. Therefore, in this review, we discuss the key factors and challenges for translating this procedure, and strategies to overcome those obstacles.

Major factors influencing PTT efficiency

It is important to note that the efficiency of PTT is influenced by two checkpoints, PTA localisation and laser incidence. Enhanced activity at the site of a solid tumour can be reached by ensuring maximal PTA concentration at the site and laser incidence tailored to achieve the desired elevation in temperature, thereby reducing risk of bystander effects. Needless to say, PTA design and laser properties play a major role in the efficiency of this therapy. Here we summarize the major considerations for these components of PTT (Fig. 2).

Table 2 | Quantitative outcomes from large animal-preclinical and clinical studies

Study Referrance	Model	PTA Type	Clinical Success Rate	Safety Profile
Preclinical study in large mammals[152]	Canine mast cell tumour	Gold-coated silicone NPs	100% response, 94% remission	No toxicity in vital parameters
Preclinical study in large mammals[153]	Canine/feline mammary	Gold nanorods	Median survival 315.5 ± 20.5 days	No toxicity, normal organ function
Clinical pilot safety study[154]	Human metastatic breast cancer	Indocyanine green (ICG)	75% clinical beneficial response rate	Favourable safety profile
Clinical trial[97]	Human prostate cancer	Gold-silica nanoshells	94% (15/16 patients)	Safe, no major adverse events

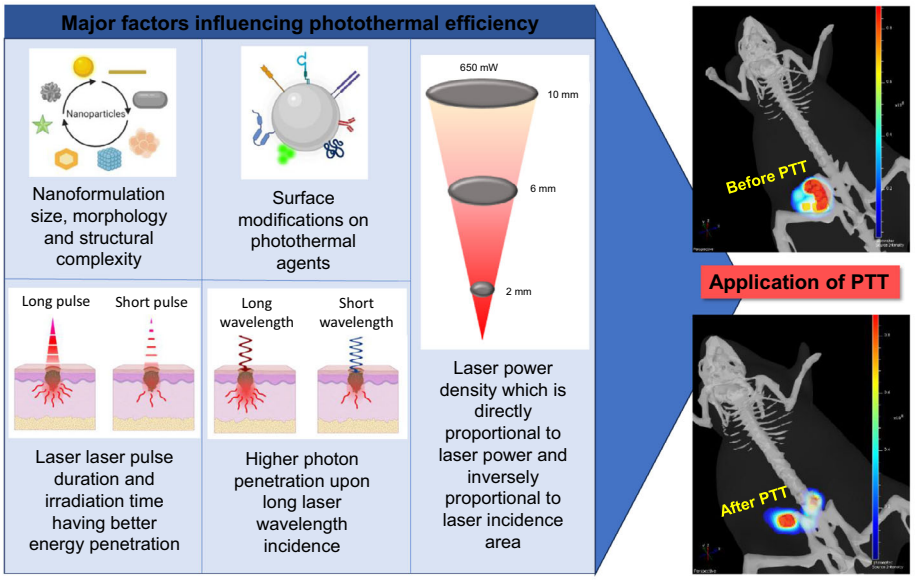

Fig. 2 | Schematic showing major factors influencing photothermal efficacy. Tumour debulking post application of PTT.

Physical properties of PTAs

The route of administration for the photothermal agent depends on the size, morphology and surface functionalisation of the nanomaterial. The size and shape of the PTAs directly affect the properties of localized surface plasmon response (LSPR)[11]. Gold nanospheres smaller than 40 nm exhibit stronger absorption in the visible to near-infrared (NIR-I) range due to LSPR, while larger nanospheres (>40 nm) predominantly scatter light[12]. However, anisotropic nanoparticles like gold nanorods (AuNRs) demonstrate distinct optical behaviour. For example, miniaturized AuNRs (5–11 nm) with optimized aspect ratios can achieve LSPR peaks in the second near-infrared (NIR-II) window (1000–1350 nm), enabling strong absorption for PTT and photoacoustic imaging[13]. These smaller AuNRs also exhibit enhanced thermal stability and photoacoustic signals due to their high surface-to-volume ratio, which improves heat dissipation and reduces structural degradation under pulsed laser irradiation[14]. Nanomaterials having branched structures exhibit LSPR peaks in the NIR region due to increased cross-sectional area for light absorption. A strong electromagnetic field develops due to the branched patterns, thus enhancing the overall light absorption. Also, the compact arrangement of the components in the nanomaterials generates a strong plasma coupling effect, which leads to a broad absorption of light in NIR wavelengths[15]. Gold nanostars with sizeable cross-sectional areas have excellent surface-enhanced Raman scattering properties for PTT and multi-modal photoacoustic imaging[16]. Alterations of surface functionalization also influence LSPR of the nanoparticles by changing the material's refractive index. This modification contributes to enhanced targeting efficiency, improved stability and light absorption efficiency, and improved photoacoustic signals for multi-modal imaging and photothermal conversion[11].

The safety and pharmacokinetics of PTT agents are critical for their clinical application, with organic agents showing significant advantages over inorganic ones. Organic photothermal agents, such as single-component organic phototherapeutic agents (SCOPAs), are highly biocompatible, biodegradable, and exhibit low systemic toxicity[17]. These materials, including near-infrared dyes like indocyanine green, can be metabolized and cleared efficiently from the body, minimizing long-term retention risks. Their modular design allow for tumour-specific activation mechanisms, enhancing therapeutic precision while reducing damage to healthy tissues[18]. For example, organic agents like aza-BODIPY derivatives leverage tumour-specific triggers (e.g., reactive oxygen species) to ensure selective activation, improving safety and efficacy in vivo[19]. In contrast, inorganic PTT agents, such as gold nanoparticles and metal-based nanomaterials, face challenges in clinical translation due to poor biodegradability and potential cytotoxicity. While these materials exhibit excellent photothermal conversion efficiency, their prolonged retention and inflammatory side effects demand selective use of the constituent material. Strategies to enhance their safety include surface modifications and combinational therapies; however, achieving regulatory approval remains challenging.

Properties of Laser

Photonic incidence used in PTT, primarily NIR range lasers, varies widely in several parameters such as laser wavelength, power density, and pulse width. The NIR wavelength range varies between 700–950 nm range is well known to confer better tissue penetration as well as higher photothermal conversion efficiency by the PTAs[20,21]. Use of NIR source in PTT is attributed to: (i) minimal photonic absorption by the tissue components; (ii) greater tissue depth penetration ability, and (iii) low toxicity due of lesser energy minimizes alteration of cellular biochemistry in tissue environment, thus rendering it a safer source than higher energy light sources like UV radiation. The choice of laser wavelength also influences penetration; for instance, lasers in the NIR-II window exhibit deeper penetration as compared to the NIR-I window, the lasers used in most of the PTT applications.

Advanced laser systems confer precisive control for illuminating a targeted area. Radiation characteristics like spectral width and laser power output are also critical to achieve efficacious therapy[22]. The power density of a laser source represents the amount of energy delivered per unit area upon laser irradiation. Lower power densities (0.12–0.22 W) coupled with

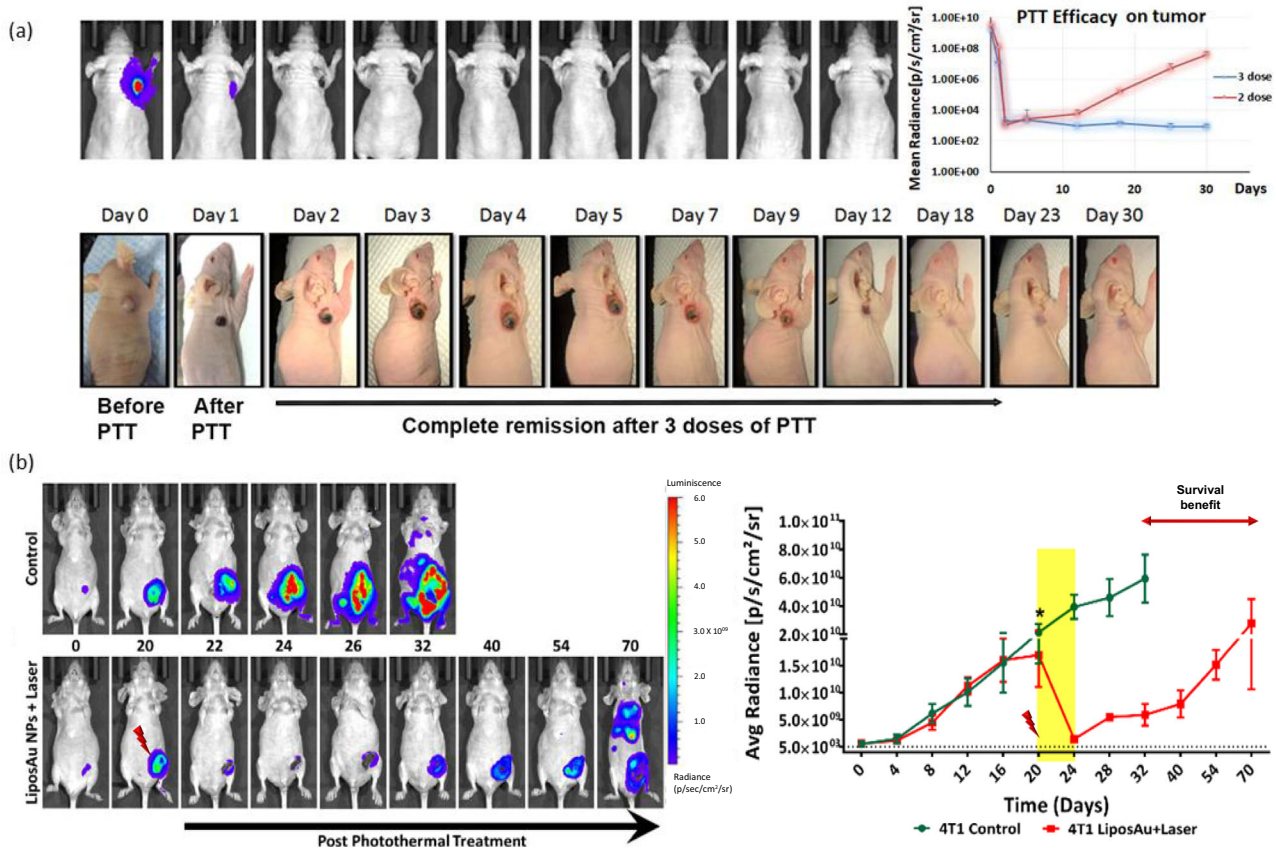

Fig. 3 | Photothermal efficiency in preclinical murine model. a Unpublished results representing PTT efficacy using preclinical xenograft tumour in an immunocompromised nude mouse. Upper series represents luciferase reporter imaging guided non-invasive monitoring of tumour growth kinetics for the first 12 days after performing 3 doses of PTT on day 1. Lower panel represents the photographic capture of the same mouse with additional follow up till day 30, **b** Representative non-invasive imaging-guided monitoring of orthotopic breast tumour xenograft-bearing mice with optimized PTT procedure performed on day 20 at the primary tumour site as indicated. Compared to untreated control mice, life expectancy doubled in PTT-treated mice.

optimized pulse durations enable deeper tissue penetration while minimizing thermal damage to healthy tissue[23,24]. High power densities (>1 W/cm²) risk collateral damage but can be mitigated using pulsed irradiation, which allows heat dissipation between pulses[25,26]. Conversely, prolonged exposure at lower power densities enhances nanoparticle accumulation in tumours via the EPR effect[27]. The laser's pulse width influences the thermal distribution in the tissue. Shorter pulse widths restrict thermal energy within target tissue, reducing bystander effects, while, longer pulse widths allow increased heat dissipation which is beneficial for deeper tissue penetration but requires careful precision to avoid non-specific side effects on adjacent healthy tissue[28]. Previously, we have shown the precision achieved in PTT-treated ex vivo tumour tissue samples using a Raman-spectroscopic map, which is based on the change in endogenous biochemical signatures[5]. Duration of photonic incidence influences heat conversion and, therefore determination of complete remission as per laser duration and doses is important. Application of non-invasive, longitudinal assessment using firefly luciferase-based bioluminescence imaging in preclinical models can be a very valuable procedure in this context, resulting a definite survival benefit (Fig. 3a-b).

Challenges of PTT application at clinical setting

In the following section, we discuss the major clinical impediments, outlined in Fig. 4, to overcome for better translation implications of PTT.

Tumour targeting strategies of PTAs

A majority of preclinical studies used intra-tumoural injection of PTA to measure the PTT effect on a palpable solid tumour. This strategy serves a preliminary testing purpose for a new PTA synthesized. The other strategy of material delivery that is also very common is based on a tumour vasculature property well characterised, i.e., the enhanced permeability and retention (EPR)[29,30]. In this strategy, commonly known as 'passive targeting', various PTAs have been designed maintaining physical parameters required for EPR. In this context, vitamin E modified Au-PLGA nanoshell (Tocophotoxil) was shown to have significant EPR mediated accumulation in subcutaneous HT1080 xenograft and 4T1 orthotopic breast tumour models, resulting in enhanced localization and tumour ablation[31]. Vitamin E derivatives enhance the EPR effect by modulating tumour vasculature. These compounds inhibit angiogenesis by suppressing vascular endothelial growth factor (VEGF) production, normalize blood vessel permeability, and increase cell membrane fluidity, facilitating nanoparticle extravasation into tumours. Additionally, its hydrophobic nature ensures stable integration into lipid layers, enabling consistent delivery of therapeutic nanoparticles to tumour sites[32]. Use of carbon monoxide (CO) has been reported to enhance EPR phenomena, where CO-carrying palladium nanosheet (PdNS-CO) augmented EPR effect, resulting in higher photothermal ablation in A549 xenograft model[33–35]. CO also enhances the EPR effect through its potent vasodilatory properties, which increase tumour blood flow and promote nanoparticle extravasation via leaky vasculature. CO also inhibits tumour cell proliferation, induces apoptosis, and modulates the immune microenvironment by reducing inflammation. The controlled delivery of CO-releasing molecules (CORMs) enhances nanoparticle accumulation at tumour sites while improving therapeutic efficacy in cancer treatment[34]. However, the point to be noted in this context is that passive uptake of nanomaterials highly varies among various tumour types and/or their tissue of origin. This heterogeneity is a function of the degree of angiogenic and lymphangiogenic vasculature, perivascular neoplasm, stromal density, intra-tumoural pressure as well as tumour immune microenvironment[36].

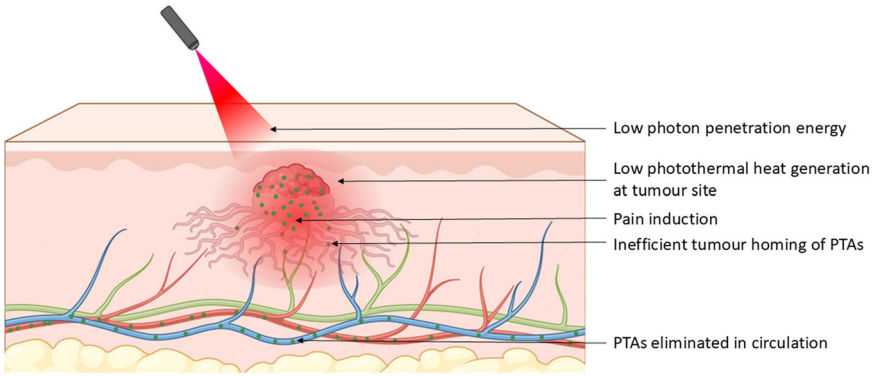

Fig. 4 | Challenges hindering translation of photothermal treatment to clinics. Inefficient homing and retention of PTAs at the tumour site, low laser penetration power, and low photothermal heat generation at the tumour site, pain induction at the treatment site.

Table 3 | Targeting strategies for tumour homing adopted by some PTAs synthesized

Nanoformulation	Targeting strategy	Reference
Cy7-TCF-IMC NPs	COX-2-mediated targeting	155
Bio-PPh3 -PT	Biotin receptor and mitochondria targeting	156
HSA/dc-IR825/GA NPs	Endocytic cell uptake and molecular targeting	157
CyT NPs	Oestrogen receptor and mitochondria targeting	158
4T1-HANG-GNR-DC NPs	Homotypic biomimetic targeting	159
HA-IR-780 NPs	HA-based tumour targeting	160
FA–NGO–PVP/DOX NPs	FA based tumour targeting	161
Ti_3C_2/Apt-M nanosheets	MUC1 tumour targeting	162
Ts-PT-RGD NPs	RGD-based tumour targeting	163

Cy7-TCF-IMC heptamethine cyanine dye linked to indomethacin, *Bio-PPh3 -PT* biotin and triphenylphosphine based photothermal agent, *HSA/dc-IR825/GA* human serum albumin- cyanine dye IR825- gambogic acid, *CyT* tamoxifen linked Cy, *4T1-HANG-GNR-DC 4T1* cloaked hyaluronic acid tagged gold nanorod with doxorubicin encapsulation, *FA–NGO–PVP/DOX* folic acid-nanographene oxide- polyvinylpyrrolidone- doxorubicin, *Ti_3C_2/Apt-M* Titanium carbide/MUC1-aptamer, *MUC1* mucin1, *Ts-PT-RGD* 4-methylbenzenesulfonamide- hemicyanine dye- RGD peptide.

For the purpose of potential clinical translation, tumour targeting efficiency (either passive or active) of the PTA from systemic circulation is a crucial evaluation. There are several aspects to judge how a PTA interacts and accumulates within the biological/physiological milieu in the body. Upon systemic administration of the PTA, the material encounters endothelial impediments such as serum proteins and opsonins within humoral circulation[37,38]. Such adsorbed components on the material surface form the particle-protein complex, commonly known as protein corona. The protein corona may get recognised by the mononuclear phagocyte system (MPS), thereby enhancing PTA clearance by the reticuloendothelial system (RES). Other than increasing the immunogenicity of the material, the presence of protein corona may also impact the size and stability of the material and consequently its pharmacokinetic properties and trafficking to the tumour site[38,39]. The third parameter that influences uptake of PTA after it intravasates at the tumour sites is intracellular interactions and uptake in the cancer cell. The high diversity among cancer cell surface receptor expression has driven various target-specific PTA design strategies to ensure uptake efficiency. Literature reported preparation of overexpressed receptor or cancer cell-specific biomarker targeted PTA development (Table 3). Further, the interaction of PTAs with the immune system in vivo cannot be ignored[40]. As many nanomaterials can act as immunomodulators, researchers must evaluate this aspect, and PTAs can be suitably modified so that they are not recognized by body's immune system. Strategies to either suppress or stimulate the immune system can also be applied to deliver PTA in a targeted manner. In a biomimetic delivery system, doxorubicin (DOX)-loaded $MnFe_2O_4$-DOX-MCM nano-cubes (NCs), camouflaged with macrophage cell membranes (MCM), enhanced immune evasion and cancer cell uptake while imparting chemo-photothermal therapy[41]. These physiological complications could be the reasons that entail why, despite avid research in this field, just a handful of PTAs have succeeded in the clinic[36,42].

Laser penetration power and photothermal heat conversion at tumour site

Photothermal ablation essentially involves NIR laser incidence over localised plasmonic nanoparticles. Use of NIR laser in PTT is important as it provides higher tissue penetration power with minimal absorption and scattering attenuation within the tumour bed. The factors affecting the laser penetration power are laser wavelength, power density and pulse width[43]. Critical optimization of these parameters can ensure targeted and controlled cell death within the tumour volume. In a study, micro-sized thin-film thermocouple (TFTC) arrays were developed and placed on free-standing Si_3N_4 thin-film windows as sensors. These sensors demonstrated linear responses in output voltage to laser power density within the wavelength range of 325–1064 nm. The sensors also provided information about the local temperature at the laser spot. Measurements taken through thick porcine tissues revealed effective single log-fold attenuation for different tissues: 5.1 ± 0.4 mm for porcine fat, 4.7 ± 0.7 mm for porcine skin-fat combination, and 3.5 ± 0.1 mm for porcine muscle[44]. In a study, Au Triangular Nanoprisms (BATrisms) modified with Leucine (L)- and lysine (K)-rich cell-penetrating peptides (LK-BATrism) were reported showing improved cell penetration and enhanced photothermal conversion efficiency using a very small dose (2.5 μg) of Au and very low power (0.25 W/cm^2) 808 nm laser[45]. Another study suggested that the use of gold nanobipyramids with an infrared absorption peak located in the NIR I window, in combination with femtosecond laser irradiation, could be an effective approach for photothermal ablation of liver cancer cells[46]. In this context, it is worth noting the development of a gold nanosphere PTA where the core material used was a thermolabile polymer composed of chitosan and poly-(N-vinyl caprolactam) (PNVCL). This material also exhibited a high photothermal conversion efficiency of 63.17% using a 750 nm laser wavelength and 650 mW laser power and therefore demonstrated high photothermal efficacy[47].

NIR wavelength has two transparency windows: NIR-I (700–900 nm) and NIR-II (1000–1700 nm). While NIR-I lasers have been majorly used for PTT, NIR-II (1000–1700 nm) also gained some attention to achieve deeper penetration and higher safety limits. The 1300–1400 nm range is preferred over 1500–1700 nm to avoid increased water absorption and minimized adverse photon scattering effects in brain tissue[48,49]. FDA has approved a 1275 nm wavelength laser for physical therapy, demonstrating its safety and efficacy for treatment of chronic pain and fibromyalgia. In an interesting study, using polyethylene glycol (PEG)-stabilized copper sulfhide nanoparticles, exhibiting similar absorption efficiency at both 808 nm and

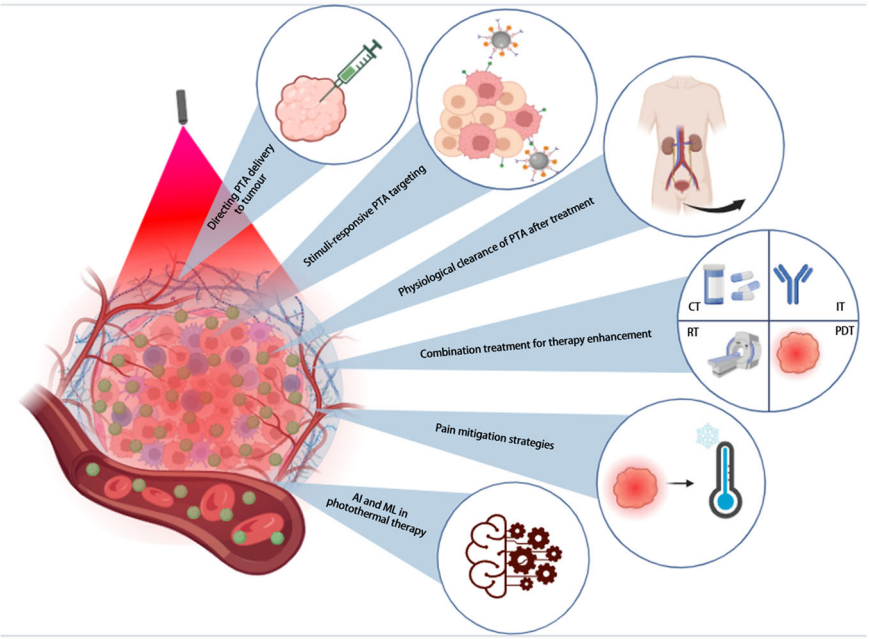

Fig. 5 | Strategies to improve clinical potential of PTT. Directing delivery of PTAs, stimuli-responsive PTA targeting, physiological clearance of PTA post-treatment, combination therapy, pain mitigation strategies and integration of AI and ML in photo-thermal therapy. CT Chemotherapy, IT Immunotherapy, RT Radiotherapy, PDT Photo-dynamic therapy, AI Artificial Intelligence, ML Machine Learning.

1275 nm wavelengths, a direct comparison between the two lasers related to the nanoparticle absorption spectrum was shown. This study reported the superiority of the 1275 nm laser in terms of temperature rise in vitro and tumour destruction in vivo[49].

Management of pain induction

Post-therapy pain management is a complex issue that involves unique sensory and emotional experiences of the patient undergoing a therapy procedure. Understanding pain perception for PTT is crucial as this process is essentially creating a burn wound at the treated site, and thereby, secondary clinical challenges may arise. The subjective nature of pain, as defined by the IASP (International Association for the Study of Pain) and WHO, is centred on individual's experience rather than just tissue damage[50,51]. This distinction between nociceptive and non-nociceptive stimuli, and how nociceptors encode these, reveals variability in pain experiences. Acknowledging patients' pain reports, regardless of origin, is vital in clinical care, reflecting the subjective nature of pain.

Monitoring the rise of temperature at the site while performing PTT is vital to ensure both treatment efficacy as well as patient comfort/discomfort. As changes in tissue temperature affect optical properties like absorption and scattering, the potential to measure temperature indirectly through monitoring alterations of physical properties has been attempted. Invasive methods like interstitial thermometry offer accuracy but cause high discomfort[51–53]. Infrared (IR) device for real-time monitoring of surface temperature at the site of treatment is commonly used. There are also MRI-based methods that relied on temperature-dependent properties like proton resonance frequency shift or T1/T2 relaxation times. This method is potentially accurate but complex to calibrate and often expensive for practical application[51,54]. Given these challenges, alternative non-invasive deep tissue temperature monitoring during PTT was attempted. It is worth noting an interesting application based on Raman spectra analysis for measurement of subsurface temperature, called Temperature SORS (T-SORS)[55,56]. Later, combining Raman signal and surface-enhanced Raman spectroscopy (SERS) nanoparticles, T-SESORS enabled deep tissue temperature monitoring and precise photothermal treatment[57]. Researchers have also developed a nanoprobe using gold nano-stars for heating and CaF_2:Nd_{3+}, Y_{3+} nanothermometers for temperature measurement, achieving real-time monitoring within tissues[58]. This work design harnessed different light windows for tracking and accurate temperature sensing, offering a resolution of around 4 °C. Such integrated approaches provide non-invasive, real-time deep tissue temperature monitoring during PTT, which is a vital step in optimizing PTT outcome.

Newer strategies adopted to improve clinical potential of PTT

Recent advances have focused on several innovative strategies to enhance the therapeutic potential of PTT while addressing key limitations. The following critical approaches target the major barriers to clinical adoption, from improved tumour targeting and precise temperature control to post-treatment considerations like agent clearance and pain management (Fig. 5).

Directing delivery of PTAs to the tumour site

The efficacy of PTT heavily relies on the concentration of PTA at the tumour site. Intra-tumour injection is effective in delivering a large amount of PTA directly to the tumour site, allowing for localized heating and tumour ablation. While direct injection localizes nanoparticles to tumour sites, uneven distribution throughout the tumour due to factors like fluid pressure and vascularization can lead to incomplete tumour ablation, increasing recurrence risks. Therefore, strategic development of PTA is crucial for PTT treatment efficacy[59]. Researchers continue to explore various strategies by attaching cancer cell surface receptor targeted antibody, peptide, etc., on PTA surface to enhance the delivery, distribution, and retention within the tumour, while minimizing systemic side effects and maximizing therapeutic efficacy. Mooney et al. addressed this by using tumour-targeting neural stem cells (NSCs) as carriers for gold nanorods (AuNRs), enhancing their distribution after intratumoural administration without compromising NSC viability. This approach reduced recurrence rates in breast cancer xenografts, surpassing direct AuNR injections in efficacy while minimizing off-target effects[60]. To enhance tumour targeting of PTA, dual-targeted photothermal agents, leveraging both extracellular as well as subcellular targets, have gained immense popularity[61]. Improving tumour specificity and the ability to navigate physiological barriers forms a critical focus in the development of the PTT nanomedicine.

Stimuli-responsive PTA targeting

In recent times, stimuli-responsive targeting in nano-formulation has gained popularity. Some of these strategies are implicated in PTAs developed as well, where the nanoparticles can respond to specific stimuli, thereby enhancing the specificity and efficacy of PTT. These responses may

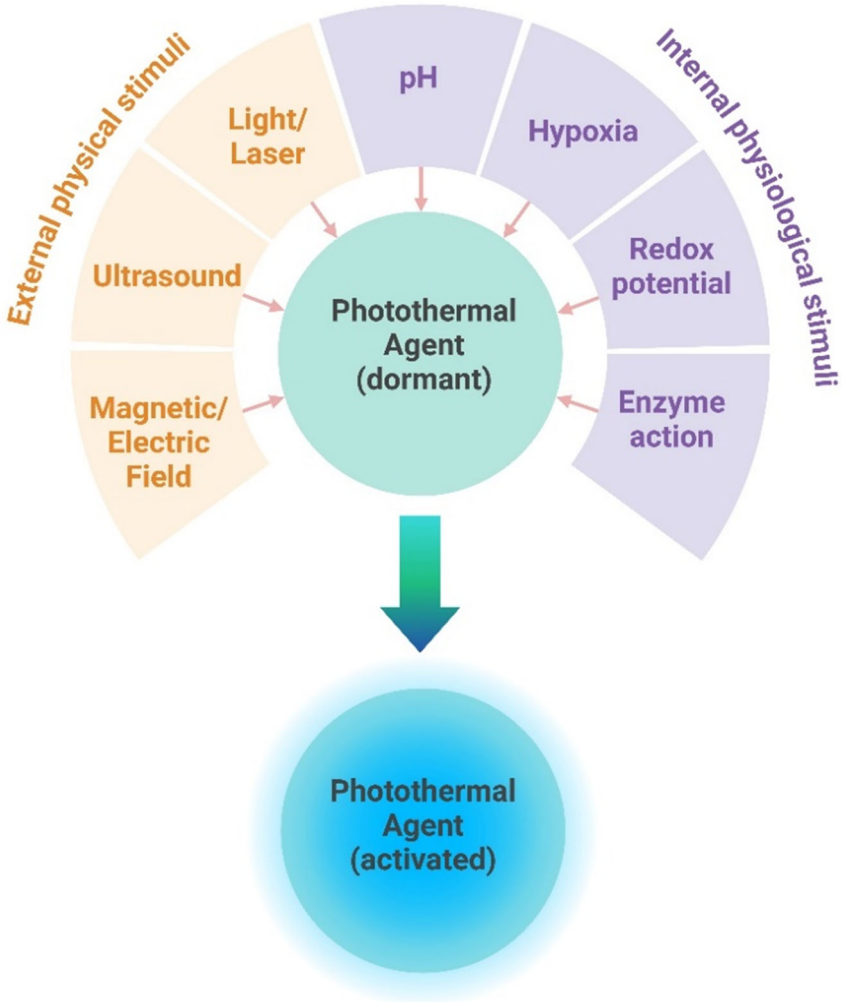

Fig. 6 | Different types of stimuli responsible for activation of photothermal agents at tumour. Impact of external physical stimuli such as light/laser, ultrasound, magnetic/electric field or internal physiological stimuli such as tumour pH, hypoxia, redox potential, enzyme action trigger activation in dormant PTAs.

be triggered by external physical stimuli, such as light/laser, ultrasound, magnetic or electric fields, or internal triggers based on tumour physiology such as pH or enzyme action. These approaches enable nanoparticles to "shield" themselves in the bloodstream and selectively activate their targeting capabilities at the tumour site[62,63]. Some common stimuli-based PTA targeting strategies are outlined in Fig. 6.

The pH-responsive NPs exploit tumour acidity to undergo changes (such as swelling, degradation, or release of payloads), enabling controlled release of therapeutic agents. In a recent study, pH-responsive perylenediimide nanoparticles (PPDI-NPs) were functionalized with a piperazine ring to enhance NIR absorption in acidic environments. The protonation of piperazine groups inhibited the photoinduced electron transfer, leading to enhanced NIRF emission at 760 nm[64]. The development of an innovative dual-stimuli-responsive theranostic nanoprobe for active tumour targeting, fluorescence imaging, and guided PTT was engineered using asymmetric cyanine and glycosyl functionalized gold nanorods (Acy and Glu@AuNRs). Higher levels of matrix metalloproteinases (MMPs) in the acidic microenvironment triggered peptide cleavage, releasing Acy, which fluoresced in the acidic environment and served the purpose of imaging. The retained Glu@AuNRs and Acy also enabled targeted PTT when exposed to an 808 nm laser. This strategy of using a cleavable peptide linker can be adapted for other tumour-specific enzymes, enhancing versatility[65]. Such programmed targeting approaches hold great promise in overcoming the challenges associated with immune recognition, aggregation, and shortened circulation time of nanoparticles, thereby improving their efficacy in targeted drug delivery and reducing off-target effects.

Physiological clearance of PTA after treatment

Post-treatment degradation and physiological clearance of PTAs is a pertinent yet often overlooked component[66,67]. These specialized materials—ranging from noble metal nanostructures and carbon-based nanomaterials to organic compounds and semiconducting polymers—undergo complex transformations once their primary therapeutic function concludes. The degradation pathways are multifaceted, involving structural decomposition triggered by repeated heating cycles, surface oxidation from reactive species generated during treatment, interactions with biomolecules in physiological environments, and enzymatic breakdown within cellular compartments[68,69]. This post-treatment evolution significantly impacts both treatment efficacy and patient safety. Here, biodegradable or thermolabile PTAs undergo controlled breakdown after fulfilling their purpose and undergo faster body clearance via the renal route. These systems often incorporate organic materials or naturally degradable polymers like PLGA or PCL that form a scaffold for active photothermal components. PLGA undergoes hydrolytic degradation, breaking down into lactic and glycolic acids, which are naturally occurring metabolites. Lactic acid is metabolized through the tricarboxylic acid cycle into carbon dioxide and water, while glycolic acid can be directly excreted or converted to glycine[70,71]. Similar biodegradable polymers include PCL, which produces 6-hydroxycaproic acid, and chitosan, which yields glucosamine derivatives[72]. Organic PTAs like indocyanine green undergo hepatic metabolism with minimal transformation before biliary excretion[73], while porphyrin derivatives are enzymatically processed into tetrapyrrole fragments eliminated through bile and urine. Even inorganic materials can be engineered for biodegradability—copper sulfide nanoparticles gradually dissolve into copper ions that bind to

transport proteins, iron oxide releases iron for incorporation into physiological iron stores, and black phosphorus degrades to biocompatible phosphate ions[74]. Excretion routes vary based on degradation product size: smaller fragments (<10 nm) undergo renal filtration[47,75], larger components follow hepatobiliary elimination, and some materials integrate into normal metabolic processes, providing multiple routes for natural elimination from the body. The temporal aspects of degradation can also be strategically leveraged for secondary therapeutic advantages, such as targeted release of encapsulated drugs or the generation of reactive oxygen species as degradation byproducts. These degradation strategies represent a significant advancement toward clinically viable photothermal therapy systems with improved safety profiles.

Combination treatment for therapy enhancement

Photothermal therapy can be significantly enhanced through both temperature modulation and combination with other treatment modalities. Mild photothermal therapy (mPTT), operating at temperatures of 42–45 °C, represents a significant advancement over traditional PTT by reducing risks to healthy tissues while breaking tumour architecture, enhancing blood perfusion, and inducing the immunosuppressive microenvironment[76]. Despite an unverified possibility of cancer cells developing thermotolerance by over-expressing heat shock proteins, strategies have been developed by including the use of advanced nanoplatforms for precise heat delivery. Meanwhile, combining PTT with other treatments amplifies therapeutic outcomes by leveraging complementary strengths.

In photoactivatable therapies, such as PDT and PTT, light illumination triggers ROS or heat generation, respectively, inside cancer cells. Significant strides have been made in understanding their biological effects inside the cellular environment or even in the tumour microenvironment, aiding clinical application. Nanoplatforms combining PDT and PTT compatible materials facilitate the synergy emerging due to their complementary mechanisms and differing toxicities, promising enhanced efficacy[77,78]. PTT enhances PDT by improving material's entry inside the cell and oxygenation through increased blood flow, while both PDT and PTT enhance ROS production and accumulation inside the cancer cells. Challenges include sequential laser irradiation due to different absorption spectra, prompting research into dual-mode agents for simplified, effective treatment[77,79,80].

The combination of chemotherapeutic drugs with PTT (CT-PTT) represents a promising strategy in cancer treatment, leveraging the synergistic effects of both modalities. Chemotherapy employs cytotoxic agents that target rapidly dividing cancer cells by inducing DNA damage, arresting cell cycles, or inhibiting oncogenic pathways. However, it faces challenges such as drug resistance and off-target toxicity. PTT causes localised heating-mediated tumour mass ablation while enhancing the capability of local drug permeability inside the tumour due to hyperthermia-induced vasodilation. This synergy overcomes PTT's light penetration issues and thereby increases the coverage area inside the treated tumour. CT-PTT combats multidrug-resistant cancer cells, improves delivery in hypoxic core of the tumours, while lowering toxicity by allowing for reduced drug doses. In a recent study, co-delivery of cisplatin with the photothermal agent PDPPDTP using biodegradable nanomicelles enhanced tumour eradication under lower drug doses[81]. Another study used methotrexate (MTX) encapsulated in polyaniline (PANI) nanoparticles, demonstrating burst drug release upon near-infrared (NIR) light irradiation, leading to enhanced apoptosis and tumour suppression[82] This dual approach enhances efficacy by targeting cancer cells through multiple mechanisms, leading to greater tumour shrinkage compared to either therapy alone.

Moreover, PTT raises tumour temperature, increasing oxygenation and sensitivity to X-ray and gamma-ray radiation, while it also impedes repair of radiation-induced double-strand breaks (DSBs), which enhances the effectiveness of radiation therapy. This integrated approach may also minimize side effects and therapy cycles, thereby promising a significant advancement in cancer treatment[77,78,83]. In recent times, combining PTT with immunotherapy has emerged as a promising approach in cancer treatment by inducing a systemic anticancer immune response. PTT and PDT cause immunogenic cell death (ICD), releasing damage-associated molecular patterns that boost tumour immunogenicity. This process can effectively activate immune cells present in the area, turning the treated tumour into an in situ vaccine. Combining PTT/PDT with immunotherapy, including immune-checkpoint inhibitors (such as anti-PD-1, anti-PD-L1, and anti-CTLA4 antibodies), amplifies the immune response, increasing cytotoxic CD8 + T cell infiltration and effector memory T cells into the tumour microenvironment. This strategy targets the primary tumour, reduces recurrence and metastasis, and holds promise for preventing future tumour development and providing a potential cure[84,85].

To overcome the bottlenecks of single-mode anti-cancer treatment methods such as PTT, PDT or others, preparation of multifunctionality composite materials may appear an attractive solution and help in providing better therapeutic coverage through such a multi-prong approach. However, such composites may also naturally suffer from complications due to a large number of confounding factors associated, which impair the progression of such complex systems to clinics[86,87]. Where a combinatorial treatment approach could compensate for the sub-optimal PTT effect and requirement of PTA dosage, alleviating potential side effects, a multifunctional material may face adversities in clinical trial entry in terms of receiving regulatory approval and/or their scale-up production scope beyond an academic laboratory.

Pain mitigation strategies

Managing pain is an important side effect that should be considered as a crucial factor for patient comfort and acceptance of photothermal treatment. Pain sensations, like stinging or burning, are common side effects of these therapies, affecting patient compliance. Nociceptors, sensing pain, are deeper within the skin layers and are stimulated by heat conduction, necessitating high temperatures (>60 °C) to induce intense pain[88]. Effective strategies include combining laser irradiation with water cooling of the skin surface to minimize pain and tissue damage caused by high temperatures. Clinical approaches involve pre-medication with anaesthetics, nerve blocks, cold air cooling, and pulsed laser irradiation. A-delta (Aδ) nerve fibres, involved in skin overheating pain, can be targeted for nerve blocking[89–94].

Clinical studies using photoimmunotherapy for melanoma, applied laser irradiation along with topical medications and anaesthetics for pain management. The visual analogue scale (VAS) measures pain intensity at points but may not capture overall pain variation[95]. In 2002, Dowlatshahi et al. treated 54 breast cancer patients using 805 nm laser via a 16 G needle inserted into tumours with sensors on the needle monitored real-time temperatures near the tumour. Treatment ceased when all sensors reached 60 °C. Skin cooling was optional for tumours close to the skin. Post-treatment, patients received oral analgesics and ice pack. In a clinical trial updated in February 2017, patients with head and neck cancer received AuroShell (TM) particles for PTT. Three groups, AuroShell-3.5, AuroShell-4.5, and AuroShell-5.0, were treated with varying particle doses and laser powers. Adverse events were documented, irrespective of their relation to treatment. AuroShell-3.5 patients reported flushing, hypoxia, hypertension, and pain. AuroShell-4.5 patients experienced hypertension, urinary tract infection, and pain. AuroShell-5.0 had minimal complications, with one patient reporting none[96]. In another trial conducted using laser-excited gold–silica nanoshells (GSNs) in 16 prostate tumour patients was delivering the NIR laser light using a water-cooled catheter. Needle thermocouples monitored temperatures of critical structures, while patients received a nerve block and continuous cooling irrigation during the procedure. Out of the 16 patients, just one patient reported temporary substernal epigastric pain linked to the cold GSN suspension[97].

Maintaining temperatures ≤ 45 °C during PTT is key to managing pain, and therefore achieving control on thermal gain of PTA material could be the key. Those materials that sharply rise to a temperature range above 60-65 °C may not be compatible from the angle of patient comfort and safety. Nanoparticles, which help achieve therapeutic temperatures with less laser pow,er reduce skin burning and normal tissue damage. Local anaesthesia is conventional for pain management during PTT but may have limited applicability. Alternative strategies like distraction techniques can complement anaesthesia, tailored to patient needs and procedural context[51,92,98,99].

Artificial intelligence and machine learning in photothermal therapy

The integration of artificial intelligence (AI) and machine learning (ML) into PTT marks a significant leap forward in precision cancer treatment. AI and ML address key challenges in PTT by enhancing the design of photothermal agents (PTAs), optimizing treatment parameters, and improving real-time monitoring. AI algorithms predict the physicochemical properties and biological interactions of PTAs, enhancing their biocompatibility and targeting efficiency[100]. ML models analyze extensive datasets to determine optimal laser parameters (e.g., wavelength, power density, duration) for specific tumour types, maximizing therapeutic effects while minimizing damage to healthy tissues[101,102]. Deep learning models process thermal profiles and infrared imaging data to optimize treatment in real-time, ensuring precise temperature modulation and protecting surrounding tissues[103]. Advanced imaging analysis powered by AI precisely delineates tumour margins, guiding more accurate PTA delivery[104]. Predictive modelling enables personalized treatment plans tailored to individual patients[105,106]. Techniques like convolutional neural networks (CNNs) and super-resolution imaging in photothermal radiometry enhance tumour characterization, improving treatment planning and monitoring[107,108]. AI also predicts patient-specific pain responses and optimizes analgesic regimens[109], while ML algorithms analyze pharmacokinetic data to predict PTA clearance rates, reducing toxicity risks[110]. Preclinical studies show that AI-driven PTT systems improve therapeutic accuracy and reduce systemic side effects[102]. As these technologies progress through clinical trials, they promise to transform PTT into a safer and more effective cancer treatment modality.

Outlook

The last two decades have seen active research growth generating diverse forms of photothermal nanomaterials. The capacity to convert photonic energy into localized heat, offering precise control over the spatiotemporal therapeutic effects, was demonstrated in preclinical small animal models. As discussed above, optimizing the PTT capabilities of these nanomaterials involves external parameters like laser localization at the surface accessible tumour site, operation parameters of the laser, i.e., power density and irradiation time, accumulation of the PTA within tumour tissue, as well as morphological factors such as the size and shape of the nanomaterials. While the external laser-based photothermal ablation has been successful in treating tumours throughout the body in preclinical mouse models, challenges arise in treating lesions located deeper than a centimetre inside. Limitations exist with the laser light-induced thermal ablation for superficial tumours, owing to the strong absorption of visible light in human tissue, posing risks to non-cancerous tissues. Tissue absorption and scatter effects naturally limit the photonic strength required for optimal heat generation. Additionally, a treatment site located in the vicinity of a major vasculature may also cause a significant impediment due to heat dissipation, resulting in sub-optimal photothermal efficiency.

Therefore, combining PTT with conventional therapy approaches was attempted by various groups, demonstrating improved tumour ablative efficacies as compared to PTT monotherapy. Functionalized nanomaterials with targeting ligands have shown potential in improving stability, biocompatibility, and specificity for tumour tissue. Sophisticated photonic delivery mechanisms are also pivotal for successful clinical transition. Challenges involving the penetration depth of laser light in biological tissues have prompted recommendations for using NIR lasers due to their reduced scattering and tissue absorption, enabling deeper tissue treatment. Strategies involving the use of fibre-optic NIR lasers, combinational PTT with surgery on laser-exposed surgical beds, and developing PTT agents optimized for NIR II (1000–1700 nm) hold promise for deeper tissue tumour treatment and imaging. The strategic co-delivery of anti-tumour agents with nanoparticle-drug delivery systems[111] or advanced drug-loaded PTT fibre-optics[112–115] requires careful consideration to maximize therapeutic effects.

As clinical transition doesn't solely rely on superior treatment efficacy, careful evaluations of multiple aspects, such as safety evaluations concerning their fate, body elimination, biodegradation, haemotoxicity, and immunotoxicity parameters of PTA should be considered[116]. Additionally, addressing tumour type and stage-specific selectivity and ways to improve their concentration at tumour sites are also crucial for enhancing therapeutic benefit. In the era of precision medicine, future applications should also carefully evaluate PTT dose requirement, patient compliance, management of pain and post-treatment long-term follow-up for clinical integration. Transitioning innovative PTT platforms, such as enhanced laser fibre optic devices and optimized PTT agents, from laboratories to the clinics demands meticulous design enhancements as well as strategic experimentations. In summary, future innovations providing more specific information on targeting and safety profiles can push the boundary, widening the scope of PTT application in the clinic.

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Competing interests

The authors declare no competing interests.

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