OXFORD

Antibody Therapeutics, 2025, 8(1), 68–85
https://doi.org/10.1093/abt/tbaf001
Advance access publication date 20 January 2025
Review Article

Near-infrared photoimmunotherapy: mechanisms, applications, and future perspectives in cancer research

Derek Allen[1], Madeline JoAnna Szoo[2,3], Tessa D. van Bergen[1], Ani Seppelin[3,‡], Jeonghyun Oh[4,‡], Mohammad A. Saad[1,*]

[1]Wellman Center for Photomedicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, United States
[2]Department of Chemical Engineering, Northeastern University, Boston, MA 02115, United States
[3]Department of Biochemistry, Northeastern University, Boston, MA 02115, United States
[4]Department of Physics, Northeastern University, Boston, MA 02115, United States

[*]Corresponding author. Wellman Center for Photomedicine, Massachusetts General Hospital, 40 Blossom Street, Boston, MA 02114, United States. E-mail: msaad1@mgh.harvard.edu.
[‡]Ani Seppelin and Jeonghyun Oh contributed equally.

Abstract

Photoimmunotherapy (PIT) involves the targeted delivery of a photosensitizer through antibody conjugation, which, upon binding to its cellular target and activation by external irradiation, induces localized toxicity. This approach addresses several limitations of conventional cancer therapies, such as chemo- and radiotherapies, which result in off-target effects that significantly reduce patient quality of life. Furthermore, PIT improves on the challenges encountered with photodynamic therapy (PDT), such as nonspecific localization of the photosensitizer, which often results in unintended toxicities. Although PIT was first proposed in the early 1980s, its clinical applications have been constrained by limitations in antibody engineering, conjugation chemistries, and optical technologies. However, recent advances in antibody–drug conjugate (ADC) research and the emergence of sophisticated laser technologies have greatly benefited the broader applicability of PIT. Notably, the first near-infrared photoimmunotherapy (NIR-PIT) treatment for head and neck cancer has been approved in Japan and is currently in phase III clinical trials in the USA. A significant advantage of PIT over traditional ADCs in cancer management is the agnostic nature of PDT, making it more adaptable to different tumor types. Specifically, PIT can act on cancer stem cells and cancer cells displaying treatment resistance and aggressive phenotypes—a capability beyond the scope of ADCs alone. This review provides an overview of the mechanism of action of NIR-PIT, highlighting its adaptability and application in cancer therapeutics, and concludes by exploring the potential of PIT in advancing cancer treatments.

Statement of Significance:
Photoimmunotherapy (PIT) is a tumor-targeted therapy with minimal off-target effects. Recent advances in technology have expanded PIT's clinical applications, including its approval in Japan for head and neck cancer treatment. This review discusses the application of PIT in cancer therapeutics and its potential in advancing cancer treatments.

Keywords: photoimmunotherapy; photoimmunoconjugates; photodynamic therapy; antibody–photosensitizer conjugates; cancer therapeutics

Introduction

The most common cancer treatment options today are chemotherapy, radiation therapy, and surgical resection [1]. However, despite the advancements made in improving these treatment options, cancer remains a massive burden on public health due to the highly adaptable nature of cancer cells, the emergence of treatment-resistant phenotypes, and adverse events associated with most treatments. There has therefore been a concerted effort to increase the efficacy of cancer killing, while simultaneously decreasing the nonspecific deleterious effects of these therapies.

A therapy that has found increasing application in cancer treatment is photodynamic therapy (PDT) [2, 3]. PDT is a light-based treatment that utilizes a nontoxic photosensitizer (PS), which, upon irradiation, induces cytotoxicity and modulates the tumor microenvironment [4, 5]. Unlike radiation therapy, PDT utilizes nontoxic wavelengths of light [usually infrared (IR) and near-infrared (NIR)]. Furthermore, PDT achieves greater specificity than radiation therapies due to preferential PS localization as a result of the enhanced permeability and retention effect, as well as confined irradiation to the region of interest. PDT has several advantages over standard therapies; radiation therapy, for example, often leads to radiation-induced fibrosis [6]. In contrast, PDT causes less damage to exposed tissues, as is observed with oral cancer, where PDT results in complete treatment and recovery of the oral mucosa without scarring [7]. This may be primarily attributed to the unique mechanism of PDT action and the secondary effects induced by PDT, as discussed later in this review. However, clinical studies with PDT have reported off-target effects that have restricted its utility in cancer treatment. For example, early ovarian cancer clinical studies with photofrin as the PS have reported cutaneous phototoxicity and bowel perforation [8–10]. Additionally, clinical studies using the PS meta-tetra(hydroxyphenyl)chlorin for the treatment of pancreatic cancers have reported gastrointestinal bleeding for tumors

Received: September 4, 2024. **Revised:** November 1, 2024. **Accepted:** January 16, 2025
© The Author(s) 2025. Published by Oxford University Press on behalf of Antibody Therapeutics.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

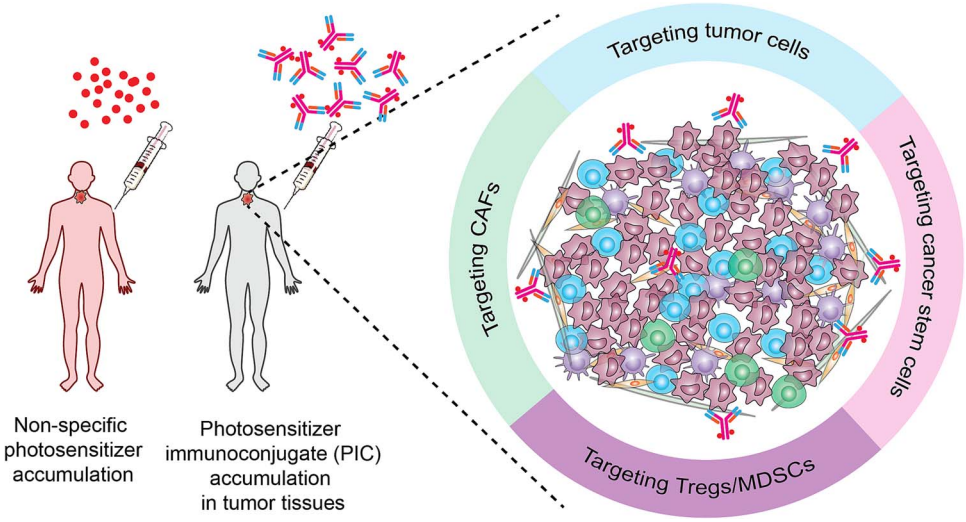

Figure 1. Tumor-targeted PIT: photosensitizer delivery through photoimmunoconjugates (PICs) results in tumor-specific accumulation. PICs can be engineered to target specific cell types in the tumor microenvironment for cancer therapeutics. So far, PICs targeted to tumor cells, cancer stem cells, cancer-associated fibroblasts (CAFs), regulatory T cells (Treg), and myeloid-derived suppressor cells (MDSCs) have been reported.

involving the gastroduodenal artery and duodenal obstruction in some patients [11]. Furthermore, while the radiation and doses used in PDT are generally nontoxic, the toxicities are usually associated with nonspecific PS accumulation and light spillage to the surrounding tissues during PDT.

The desire for more specific treatment options has led to the development of targeted therapies by targeting cells via specific markers overexpressed on their surface [12]. This can be achieved through antibodies, nanobodies [13], small molecules [14], polymers, and other targeting moieties [15]. When these targeting agents bind cancer cells, they can block biological signaling processes, alter cellular physiology, or hinder angiogenesis to decrease cancer proliferation [16]. Targeted therapeutics are developed by conjugating a cytotoxic drug to a targeting moiety to form antibody–drug conjugates (ADCs) [16]. Clinically, when conjugated with the targeting moiety, chemotherapeutic agents demonstrate improved efficacy and tolerability [17]. In total, 15 ADCs have been Food and Drug Administration (FDA) approved, and >100 are currently involved in different phases of clinical trials [18, 19]. Other targeted drug conjugates utilizing polymers (e.g. Poly [Lactic-co-Glycolic] Acid, etc.), liposomes, and nanobodies have also shown promising results in several preclinical studies [20–22]. In the context of PDT, PS-based targeted conjugates, which will be referred to as photoimmunoconjugates (PICs) for the remainder of this review, have been developed and utilized for photoimmunotherapy (PIT) as early as the early 1980s [23] (Fig. 1). An appealing aspect is the additional degree of selectivity conferred by the light dependency of PIC activation, which minimizes offsite toxicities significantly [24, 25]. PIT can be defined as a treatment that combines photodynamic therapy with immunotherapy to selectively target and kill diseased tissues through photodynamic activation of the PS via irradiation at a specific wavelength of light. In addition, the induction of immunogenic cell death and the ability to induce robust systemic antitumor immune responses has proven effective at managing both local and metastatic disease [26]. Lastly, there are emerging data on the effect of PIT on the tumor microenvironment that suggest that increased vascular permeabilization and stromal modulation can enhance the delivery of therapeutics and promote self-delivery to the target site, which could further improve the effectiveness of combination treatments [27, 28].

This review will focus on the use of PIT for cancer treatment. While advancements in light sources and light delivery technologies have greatly benefited, the field limitations in the penetration of light have been mostly countered by the use of PSs absorbing in the NIR region. Specifically in this review, we will focus on near-infrared (NIR) PIT due to the greater penetration depths afforded by light of that wavelength range and its increasing clinical use. With the recent clinical approval of PIT for head and neck cancers in Japan, and the ongoing clinical studies exploring the potential of PIT in combination with immune checkpoint inhibition (NCT04305795), there has been a renewed interest in this field. This review describes the synthesis and design strategies for PICs and the mechanism of action of PIT in treating tumor cells and other important cell types in the tumor microenvironment. We also discuss the synergistic potential of PIT with pre-existing cancer treatments to form clinically relevant combination therapies. We conclude by sharing perspectives on ongoing research and future directions in the field, as well as making a case for the development of PIT for the treatment of solid tumors.

Photochemistry and photobiology of photoimmunotherapy

Upon irradiation with an appropriate wavelength of light, mostly corresponding to the Q-band in the absorption spectrum of the PS, the PS undergoes a photophysical reaction [29], resulting in an intermediate partially stable excited triplet state. Energy or electron transfer from the PS in the excited triplet state to nearby biomolecules results in the formation of reactive molecular species (ROS) including singlet state oxygen, peroxides, and hydroxyl radicals [4, 29]. In the regions where these short-lived ROS are created, there is significant phospholipid peroxidation of membranous lipids and structural protein damage which leads to cell death through various pathways including apoptosis, necrosis, autophagy, and paraptosis (Fig. 2A) [30–33]. This differs from radiation therapy, where cell death is induced by DNA damage [29, 34]. However, achieving PS buildup specifically at the tumor site can be a challenge [35], and off-target toxicity is frequently observed in surrounding tissues. To improve the specificity of PDT, various methods have been explored ranging

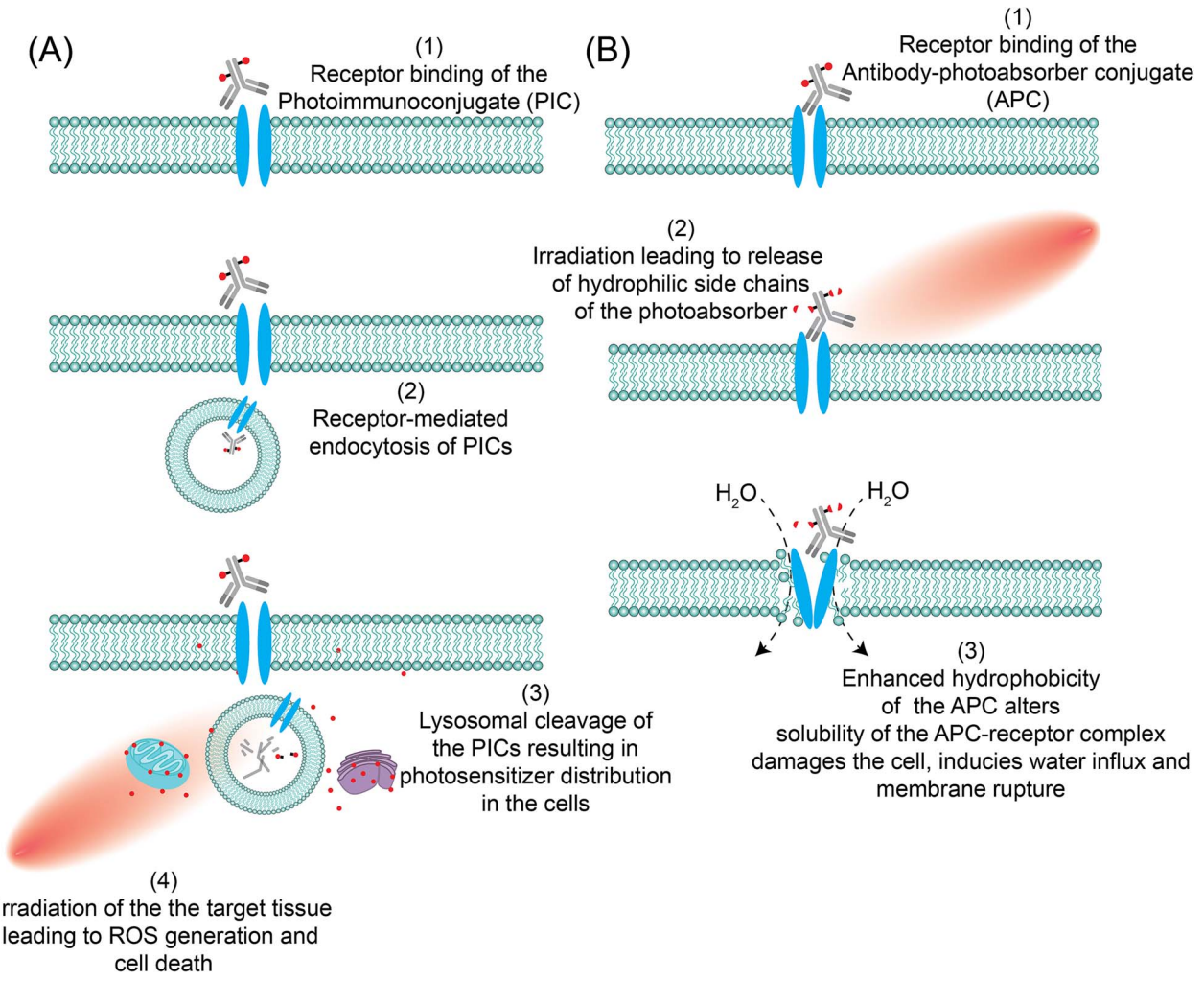

Figure 2. Comparing the two major mechanisms of action proposed for PIT. (**A**) When a photoimmunoconjugate (PIC) binds to its cognate receptor, it gets internalized through receptor-mediated endocytosis. The internalized PIC is degraded over time releasing the photosensitizer which translocates to other subcellular organelles. Irradiation at this time point leads to ROS generation and damage of subcellular organelles resulting in cytotoxicity. This mechanism is proposed for most PSs and IR700 conjugated peptides, and antibodies localized in the lysosomes. (**B**) Antibody–IR700 conjugates function through a distinct mechanism which involves (1) binding to their cognate receptors, (3) irradiation of IR700 using 690-nm light leading to the release of hydrophilic side chains of IR700 thereby increasing the hydrophobicity of the rest of the molecule, (3) aggregation of the APC–antigen complex damaging the cell membrane and resulting in water influx followed by cellular rupture.

from the conjugation of PS to antibodies or the encapsulation of PS in targeted polymeric nanoparticles [36, 37]. While the general mechanism of PDT action remains the same for most of these PS formulations, PDT using the PS, IR700, conjugated antibodies has been established to work through an entirely different mechanism [38]. Commonly referred to as the antibody–photoabsorber conjugate (APC), antibody–IR700 conjugates bind to their cognate receptors that are overexpressed on the target cell surface [39]. Following selective binding, irradiation of IR700 using 690-nm light releases the hydrophilic side chains of IR700, increasing the hydrophobicity of the rest of the molecule [38]. This enhanced hydrophobicity alters the aggregation and solubility of the APC–antigen complex thereby damaging the cell membrane, which induces water influx and ultimately ruptures the cell (Fig. 2B) [38, 40]. Cytotoxicity by ROS generation has also been reported for antibody–IR700 and peptide–IR700 conjugates that have localized in the lysosomes at the time of irradiation [41]. In addition to the damage to target cells, NIR-PIT has been reported to enhance the permeability of tumor tissues, which improves drug distribution and efficacy. This has been attributed to the super-enhanced permeability and retention (SUPR) effect, brought about by the cell death of perivascular cancer cells creating space between the remaining tumor region and the vessels; this leads to vessel enlargement, increased blood volume, as well as decreased blood velocity and vascular resistance [42]. Similar effects of enhanced tumor permeability have also been associated with conventional PDT where several studies have demonstrated increased drug uptake and distribution after PDT treatment, primarily due to alterations in the tumor vasculature and extracellular matrix [43–45].

Additionally, PIT-mediated cell death has been shown to produce damage-associated molecular patterns, which can stimulate pattern-recognition receptors in antigen-presenting cells and immune cells thereby eliciting an immune response [46, 47]. A unique attribute of PDT over other therapeutics is the effect of low PDT doses (a product of PS concentration and light dose), which results from variations in PS distribution and heterogeneity in photon distribution in a solid tumor [48]. Low-dose PDT, also referred to as photodynamic priming (PDP) [28], does not induce cytotoxicity, but results in transcriptomic, proteomic, and

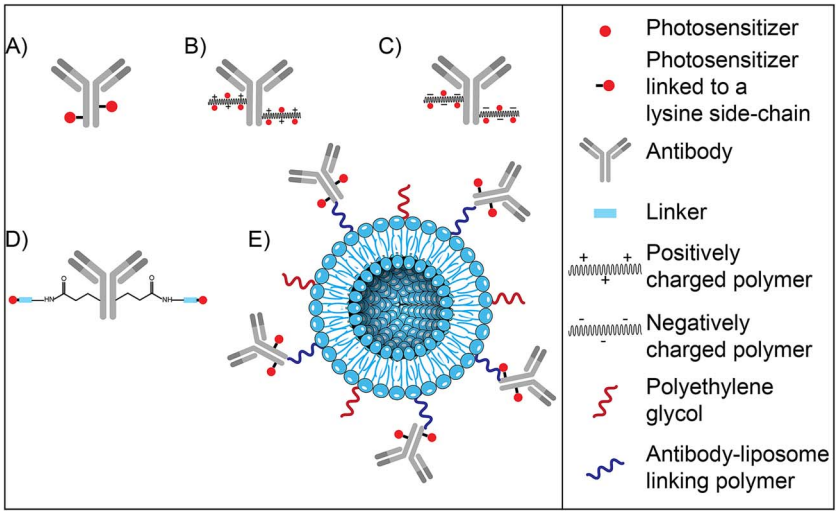

Figure 3. PIC design strategies: (**A**) PICs with stochastically conjugated PSs, (**B** and **C**) PICs with indirect conjugation through a positively and negatively charged polymer. (**D**) Direct conjugation of PSs to specific sites on the antibody and (**E**) conjugation of PICs to nanoformulations.

metabolic modulation [49] which can sensitize target cells to subsequent therapies [50].

Design strategies for photoimmunoconjugates

While PICs provide much-needed specificity in PDT applications, they are less efficient in delivering PSs to the target cells and therefore require higher light doses to achieve similar therapeutic outcomes [51]. To circumvent this issue, several strategies have been evaluated to enhance response to PIT either by improving cellular uptake of PICs or increasing loading ratios (i.e. the number of PS molecules per antibody). Some of these strategies are described below (Fig. 3).

Indirect conjugation to enhance cellular uptake of PS

Currently, most PS conjugation strategies employ direct attachment of the PS to the antibody; however, several indirect conjugation strategies have been explored as well. These include attaching the PS to charged polymers such as polyglutamic acid [52, 53], poly-lysine [54, 55], or HPMA (*N*-(2-hydroxypropyl) methacrylamide) [56, 57] for initial PS loading followed by conjugation of the PS–polymer conjugate to monoclonal antibodies. The major advantage of these techniques has been achieving a high PS-to-antibody ratio while preserving antibody specificity. However, issues related to reproducibility and purifying the PICs have limited their use. In addition, studies utilizing the well-established biotin–avidin chemistry for PS–monoclonal antibody conjugation [58], SNAP-Tag Conjugation strategies [59], and several others [60] have been performed; while there have been certain advantages associated with these conjugation strategies, the complexity of the associated reactions has so far limited their clinical translation [60].

Site-specific conjugation for enhancing therapeutic efficiency

Nonspecific conjugation by well-established carbodiimide crosslinker chemistry is frequently used for developing PICs [60]. These methods have certain limitations, including variability in labeling locations leading to differences in target specificity. To circumvent this, several strategies for site-specific labeling have been proposed [60], and several ADCs with site-specific conjugation have been approved for clinical use [61]. Site-specific chemistries provide the much-needed homogeneity and consistency in PIC preparations that may be important for clinical adaptation. For example, copper-free strain promoted alkyne-azide cycloaddition chemistry was utilized for site-specific conjugation of more than four porphyrin molecules per antibody [62]. The phototoxicity achieved using this PIC was significant, even though broad-spectrum light at a low dose of 20 J/cm^2 was utilized [62]. In a recent study, Sidiki *et al.* proposed site-specific conjugation of fluorophores on cetuximab [an anti-epithelial growth factor receptor (EGFR) antibody] which showed a 2.3-fold increase in targeted EGFR binding as compared to nonspecific labeling methods [63]. However, the utility of this chemistry for PIC synthesis and its subsequent phototoxicity must be explored further.

Optimizing PS loading ratio imparts new features

Despite advances in the field of ADCs, there is no ideal drug-to-antibody ratio or PS–antibody loading ratio that has been established. However, it has been reported that increasing the loading ratio may alter antibody specificity, induce aggregation, and change pharmacokinetics, whereas decreasing the loading ratio can reduce treatment efficacy. Pharmacokinetics in general is dictated by the larger molecule in the ADC, which in most cases is the antibody, but increasing the loading ratio can also be impactful. Savellano *et al.* reported a decrease in the specificity of the cetuximab–BPD conjugate with an increase in payload beyond 10 benzoporphyrin derivative (BPD) molecules per cetuximab molecule [64]. At a payload of 7 BPD per cetuximab, the conjugate was not only able to retain specificity and enhance BPD uptake in the cells as compared to lower loading ratios [64, 65], but also demonstrated self-quenching of PS fluorescence. Dequenching of PS fluorescence was observed upon cellular internalization and lysosomal cleavage of the PIC, thereby imparting it with tumor-activatable features. Tumor-targeted activatable PIT was thereafter exploited for imaging and image-guided therapy of preclinical micrometastatic ovarian tumor tissues [24]. A similar PS–antibody conjugate composed of cetuximab and IR800 was reported by Nguyen *et al.* [66] This study demonstrated that increasing the PS loading ratio to 10:1 from the clinically utilized ratio of 2:1 can impart tumor-activatable properties due to quenching-dequenching and enhanced PS delivery to the cell [66]. While there is no conventionally established loading ratio,

there are advantages to increasing loading, provided the antibody specificity is not altered.

Charged PICs for enhancing PS uptake

The specificity and cellular internalization of PICs can be altered by conjugating charged moieties to the antibodies, making them either cationic or anionic [67]. The use of poly-L-lysine as a linker to conjugate PSs to antibodies increases the specificity of PICs by keeping the structure of the conjugate similar while allowing for the modification of molecular charges [55]. PICs with cationic and anionic charges have been shown to behave differently with respect to target internalization and phototoxicity. In a study by Hamblin *et al.*, cationic PICs demonstrated 17-times higher *in vitro* cellular uptake of chlorin e6 as compared to anionic PICs [54]. Furthermore, cationic PICs had a higher tumor selectivity and delivered a higher PS (chlorin e6) amount per gram of tumor in a xenograft model of ovarian cancer [67]. In contrast, an *in vivo* study by Hamblin *et al.* on murine hepatic metastasis of colorectal cancer model showed that anionic PICs were more efficient (5-fold) in delivering PS to the tumor as compared to the cationic PICs [68]. These conflicting findings demonstrate the importance of administration mode where charge can play an important factor in influencing tissue distribution. Hamblin *et al.* followed an intravenous route for PIC administration, and PICs showed a higher uptake in the lungs, whereas Duska *et al.* followed an intraperitoneal administration route where the PICs may have had direct contact with micrometastatic tumor nodules and hence exhibited lower nonspecific distribution [67]. These studies demonstrate the importance of charge while designing PICs which should be optimized based on the application [69].

Nanotechnology for enhancing cellular uptake

Like many other methods, a persistent challenge for PIT is the limited amount of PS delivered to the target cancer cells through PICs. A method to improve drug delivery and uptake within the cancer cells is the use of nanoparticles (NPs). Integrating PICs with biocompatible NPs creates a PIC-nanoparticle (PIC-NP), which combines the selectivity of PICs with the improved pharmacokinetic features of NPs. In addition, conjugation of PICs to NPs has also been demonstrated to deliver a significantly higher amount of PS to target cells through what is referred to as the carrier effect [25]. The higher PS delivery achieved through these PIC-NPs resulted in higher phototoxicity not only *in vitro* but also with *in vivo* xenograft mouse models of epithelial ovarian cancer [25]. While nanoparticles in general have limited bioavailability in tumor tissues following systemic administration, the ability of PDT to modulate tumor permeability, including the SUPR effect associated with PIT, as mentioned earlier, can enhance tumor uptake and distribution of NPs and enhance treatment efficacy [42, 43, 70, 71].

Tumor-targeted photoimmunotherapy

Targeting tumor cells

Genetic and epigenetic alterations during oncogenesis can lead to the expression of mutated genes and the amplification and subsequent overexpression of cancer-associated genes. This leads to cancer cells exhibiting a distinct array of antigens intracellularly and on their surface. These antigens are known as tumor-associated antigens (TAAs) in normal tissue or tumor-specific antigens in precancerous and cancerous cells, and while their function is to support the rapid proliferation needs of these transformed cells and impart resistance to various therapies, they also allow cancer cells to gain selectivity for directing toxic agents to the target cells. Initial studies on receptor targeting were aimed at blocking these receptors to suppress proliferation and induce cell death [72]. With advancements in chemical technologies, cytotoxic drugs were conjugated to these antibodies to specifically deliver the payload to the antigen, thereby minimizing off-target cytotoxicity. In some cases, the targeting moiety and the therapeutic payload have been demonstrated to synergize and enhance therapeutic efficiency, as has been demonstrated in the case of PDT and cetuximab [73]. Several tumor cell surface receptors have been targeted for PIT including EGFR, human epidermal growth factor receptor 2 (HER2), prostate-specific membrane antigen (PSMA), folate receptor, and cancer antigen-125 (CA 125) among others [53, 74–76] as well as other intracellular targets [77]. In this section, we discuss studies about PIT involving some of the frequently targeted receptors.

Epidermal growth factor receptor

Growth factor receptors are frequently overexpressed in cancer, making them important targets in cancer treatment. The EGFR family of receptors is one of the most ubiquitously altered genes in human cancer. For example, in head-and-neck squamous cell carcinomas (HNSCCs), EGFR is overexpressed in ~80%–100% of cases [78]. EGFR is also altered in 70%–90% of ovarian cancers [79] and 74% of bladder cancers [80]. Upon ligand binding to EGFR, different pathways controlling a host of cellular processes related to growth and motility are activated [81]. EGFR overexpression thus promotes cell growth, resistance to apoptosis, angiogenesis, and cell migration. Due to its ubiquitous expression in cancer, EGFR has been a target of many cancer drugs, and three different human EGFR targeting monoclonal antibodies have been approved for use by the FDA [82]. While EGFR-targeted ADCs have shown promise in preclinical and early clinical studies, they have encountered significant challenges, mostly related to off-target toxicities, that have limited their clinical approval [83]. Since EGFR is highly expressed in HNSCC and HNSCC sites are easily accessible by irradiation, EGFR-targeted NIR-PIT in HNSCC has been the torch bearer of NIR-PIT in the clinic with a clinical trial (RM-1929-101) carried out in 2019 on patients with locally advanced and unresectable HNSCC [84]. In part 1, nine patients received either 160, 320, or 640 mg/m^2 of RM-1929 intravenously over a span of 2 h, and ~24 h post-drug administration the patients received one cycle of near-infrared light illumination. Dose-limiting toxicity did not occur at any dose, and response was only observed in one patient of the 640-mg/m^2 dose group. Currently, ASP-1929—a cetuximab–IR700 conjugate and successor to RM-1929—is being evaluated in a global multicenter phase III randomized trial for locoregional recurrent HNSCC in patients who have failed or progressed after at least two other lines of therapy (NCT03769506). Pending the results of this study, ASP-1929 has been conditionally approved in Japan in 2020 for the treatment of recurrent HNSCC [85].

For NIR-PIT, using IR700 conjugated to a single-chain variable fragment antibody against EGFR, as opposed to monoclonal antibodies, has also shown promising results in clearing human melanoma cells *in vitro* [86]. The use of antibody fragments could be beneficial compared to antibodies due to efficient solid tumor penetration and rapid renal filtration. Furthermore, a study by Jin *et al.* compared NIR-PIT targeting two separate cancer cell markers, EGFR and CD44. Through *in vivo* imaging and tumor growth monitoring of human xenograft nude mice model, it was observed that EGFR-targeted NIR-PIT had an increased tumor-to-normal ratio and a decrease in tumor growth compared to CD44-targeted

NIR-PIT [87], demonstrating the importance of antigen selection for PIT. EGFR-targeted NIR-PIT also displays efficacy in treating metastatic cancer. In one study, a bone metastasis model from a human triple-negative breast cancer cell line was established using the caudal artery injection method in an athymic mouse model [88]. Not only did NIR-PIT lead to a significant decrease in tumor size, but it also restored the bone cortex from the injuries brought about by the tumor.

Overall, EGFR-targeted NIR-PIT is a promising and well-tolerated therapy for the treatment of a wide variety of cancer types, particularly HNSCC. Pharmacological primate data suggest no toxic effects for doses up to 80 mg/kg (alternatively ~1000 mg/m^2) on the nervous, cardiovascular, and respiratory system [85]. While this may be in contrast with the several EGFR-targeted ADCs that have shown significant toxicity in clinical studies, the relative low toxicity of EGFR-targeted NIR-PIT is possibly due to its low dark toxicity and the ability to confine phototoxicity to regions that are irradiated. As the list of approved antihuman EGFR therapeutic antibodies is expanding with the aim of reducing their nonspecific toxicities, EGFR-targeted PIT will become more efficacious and may be expanded to other tumor types as well.

Human epidermal growth factor receptor 2

Similar to EGFR, HER2 is a receptor tyrosine kinase used as a therapeutic target for NIR-PIT [74]. HER2 is aberrantly expressed in a wide array of cancers including breast cancer, gastric cancer, bladder cancer, and lung cancer [80, 89]. Human HER2 targeting NIR-PIT studies using the monoclonal HER2 antibody trastuzumab have shown some degree of antitumor effect on various cancer types, including bladder cancer [89], gastric cancer [90], lung metastasis [91], and bile duct cancer [92]. Importantly, HER2-targeted NIR-PIT was also found to be effective on chemotherapy-resistant tumors which showed higher HER2 expression after acquiring cisplatin resistance [93].

In another experiment, a combination of NIR-PIT targeting EGFR (panitumumab) and HER2 (trastuzumab) was used to treat a human bladder cancer xenograft model [89]. An increase in NIR-PIT efficiency in the form of reduced tumor growth was observed compared to the monotherapies, but toxicity was also observed; 4 out of 11 mice died within 48 h after combination treatment using a light dose of 100 J/cm^2. This toxicity was proposed to have been caused by massive tumor necrosis and tumor lysis syndrome leading to a systemic inflammatory response. When conjugated to trastuzumab, other PSs—chlorin e6 and porphyrin—have also shown antitumor effects with regard to growth inhibition in murine models bearing human xenografts of breast cancer [94] and gastric cancer [95].

Prostate-specific membrane antigen

Besides NIR-PIT targeting HER2 and EGFR, other TAAs have also been targeted, such as PSMA. PSMA is a type 2 integral membrane glycoprotein that is a well-established marker of prostate cancer and is overexpressed in nearly all prostate cancer cases [96]. PSMA is also being recognized as a target for positron emission tomography (PET) (PSMA-PET) for the treatment and diagnosis of prostate cancer and metastasis. Using a human anti-PSMA IR700 conjugate, NIR-PIT was performed weekly for up to 3 weeks on athymic nude mice injected dorsally with PC3 cells that express PSMA [97]. Repeated NIR-PIT resulted in a significant prolongation of survival and a significant reduction in tumor growth, which suggests that this technology would also be effective in humans.

Targeting cancer stem cells

A subpopulation of cells that have been suggested to be the cause of treatment resistance and tumor recurrence are cancer stem cells (CSCs). Two well-established markers of CSCs are CD44 and CD133, and increased levels of both CD44 and CD133 correlate with aggressive tumors, increased cell proliferation, and poor prognosis [98]. CD44 has a role in promoting matrix-derived survival signals, cell migration, and intercellular adhesion, whereas CD133, also known as prominin-1, is believed to play a role in preserving stem cell characteristics. CD133-targeted NIR-PIT on human glioblastoma patient xenograft–derived subcutaneous tumors and U251 orthotopic glioma tumors showed a significant reduction of tumor growth and an increase in survival [99]. Alternatively, CD44-targeted NIR-PIT in syngeneic mouse models of oral cancer, colon cancer, and lung cancer has shown significant increases in survival and suppression of tumor growth [90, 100, 101]. Complete remission of the tumors was not achieved with CD44-NIR-PIT monotherapy. However, combination of CD44-NIR-PIT with CD25-targeted NIR-PIT (a regulatory T-cell marker) [102], CTLA4-targeted NIR-PIT [103], and anti-PD-1 [101] have shown complete remission in some preclinical studies. Although NIR-PIT targeting of oncogenic cell markers is a promising approach, this strategy can have unintended consequences. For example, CD44 is also expressed on local antigen-presenting dendritic cells, which are important for inducing an anticancer immune response [92]. This is particularly problematic given that the induction of the immune response after NIR-PIT is dependent on dendritic cells' activation of cytotoxic T cells [104]. Ultimately, because there is typically an overlap in antigen expression between cancer and noncancer cells, the systemic effects of PIT on the surrounding cells in the tumor microenvironment must be optimized further to limit adverse effects.

Targeting cells of the tumor microenvironment

PICS may be used to target a variety of different cell types within the tumor microenvironment (TME). While tumor cells and CSCs have historically been the primary focus for PIT, recent research surrounding the role of supporting cell types in maintaining the tumor niche and regulating responsiveness to treatment has expanded the application of this technology. Today, there are a plethora of preclinical studies, leveraging the targeting and therapeutic capabilities of PICs for a variety of cell types [105]. Most notably, as mentioned earlier, the approval of cetuximab saratolacan (RM-1929) containing IR700, and the tumor-targeting EGFR antibody, cetuximab, for the treatment of head and neck cancer in Japan has propelled research in this field [105]. While RM-1929 is still in phase III trials in the USA for head and neck cancer, a similar PIC targeting the CD25 receptor on regulatory T (Treg) cells in the TME is under consideration for clinical evaluation (NCT05220748)—(Table 1). This PIC, RM-1995, consists of IR700 and the CD25-antibody to target and deplete intratumoral Treg cells [106]. Beyond Tregs, the most frequently targeted components of the TME include other cells that mediate immune suppression including cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). These are depicted in Fig. 4 and discussed in some detail below.

T regulatory cells

Tregs are CD25$^+$CD4$^+$ Foxp3+-expressing cells that exert an immunoevasive and immunosuppressive influence in the TME by inhibiting the function of local cytotoxic CD8$^+$ T cells and

Table 1. List of PIT clinical trials

NCT number	Study title	Study status	Conditions
NCT05265013	ASP-1929 Photoimmunotherapy combined with pembrolizumab in patients with recurrent head and neck cancer, with or without metastases	Terminated	Head and neck cancer
NCT05182866	ASP-1929 Photoimmunotherapy (PIT) study in patients with recurrent head/neck cancer	Active not recruiting	Head and neck cancer Squamous cell carcinoma of head and neck
NCT03769506	ASP-1929 Photoimmunotherapy (PIT) study in recurrent head/neck cancer for patients who have failed at least two lines of therapy	Recruiting	Head and neck cancer
NCT05220748	RM-1995 Photoimmunotherapy, as monotherapy or combined with pembrolizumab, in patients with advanced CuSCC and HNSCC	Withdrawn	Cutaneous squamous cell carcinoma Head-and-neck squamous cell carcinoma
NCT04305795	An open-label study using ASP-1929 photoimmunotherapy in combination with anti-PD1 therapy in EGFR expressing advanced solid tumors	Active not recruiting	Recurrent head-and-neck squamous cell carcinoma Metastatic head-and-neck squamous cell carcinoma Locally advanced cutaneous squamous cell carcinoma Metastatic cutaneous squamous cell carcinoma
NCT02422979	Study of RM-1929 and photoimmunotherapy in patients with recurrent head and neck cancer	Completed	Recurrent head and neck cancer

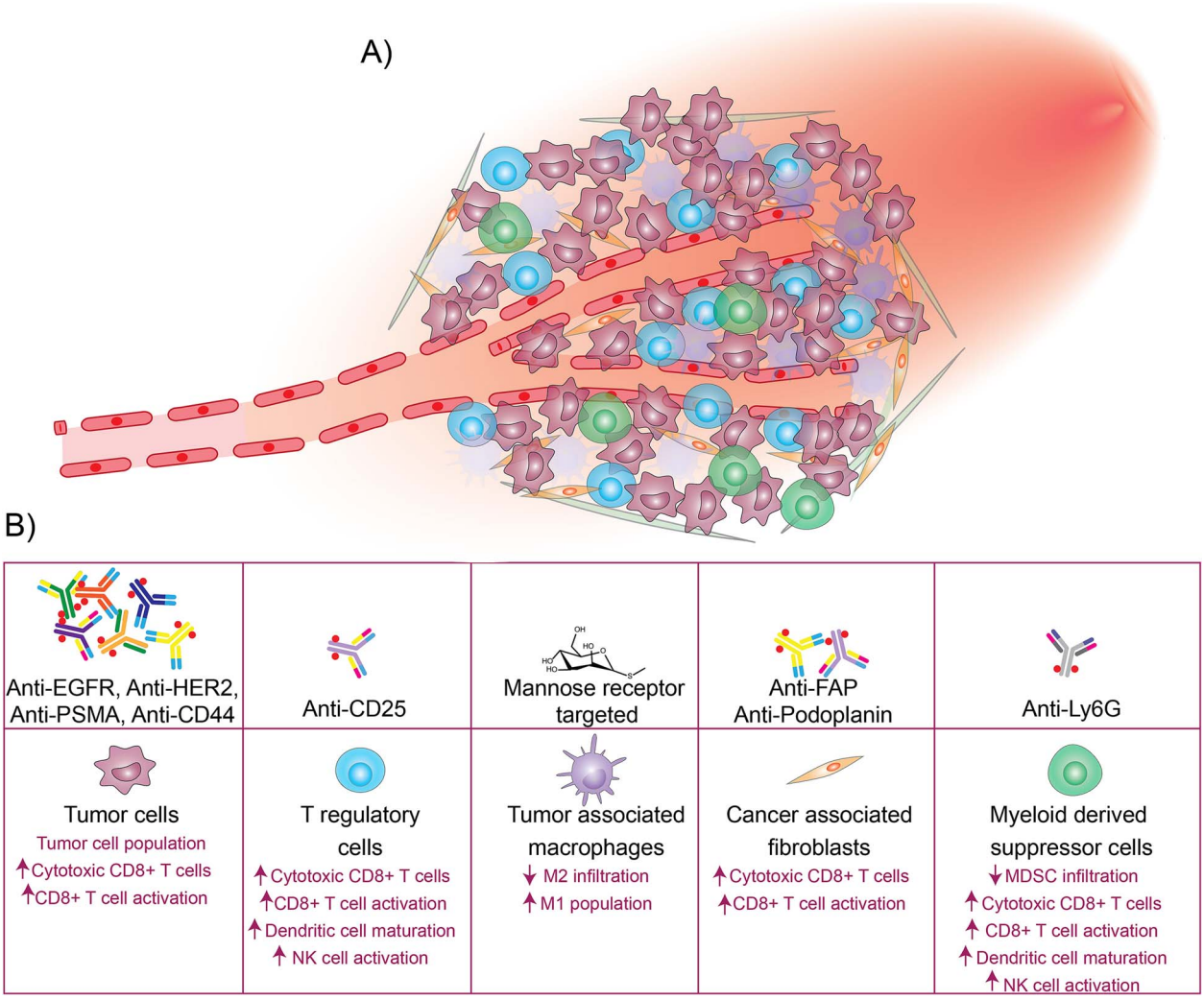

Figure 4. PIT of tumor microenvironment—(**A**) diagrammatic representation of PIT of the tumor microenvironment. (**B**) Antibodies reported for PIT of different cells in the tumor microenvironment and the corresponding treatment outcome of PIT directed against these cell types.

natural killer cells, as well as dendritic cell maturation [102, 107, 108]. Previously, Treg depletion has been achieved by intratumoral injection of anti-CD4 or anti-CD25 antibodies [107, 109]. However, the systemic administration of neutralizing antibodies can activate or exhaust other immune cells, so a more selective option is desirable [110]. NIR-PIT utilizing IR700 has largely dominated efforts to target Tregs with cytotoxic T-lymphocyte antigen 4 (CTLA4) or CD25-targeted antibodies [102, 103, 108, 110]. CD25-targeted NIR-PIT has proven to be a promising and selective approach for the depletion of Tregs, as a significant proportion of intratumoral cytotoxic T cells and natural killer cells do not express CD25 [108, 110]. Two FDA-approved anti-CD25 monoclonal antibodies, daclizumab and basiliximab, are commonly used for CD25 targeting [111–113]. However, there are concerns that CD25-targeted NIR-PIT may block the interleukin-2 (IL-2) receptor of effector T cells which are responsible for the proliferation of immunostimulatory cells [110]. To address this obstacle, conjugated anti-CD25-F(ab′)$_2$ fragments that lack the Fc region of the antibody have been evaluated; the shorter half-life of these formulations lowers the potential for receptor inhibition but maintains the targeting capabilities of the unmodified anti-CD25 antibody [110]. Ultimately, Okada *et al*. demonstrated that the anti-CD25-F(ab′)$_2$ fragments achieved significantly longer survival compared to the IgG-PIT control group, with an increase in median survival from <40 days with IgG-PIT to >80 days in a unilateral tumor and 60 days in a bilateral tumor model with F(ab′)2-PIT following exposure to NIR light (690 nm, 150 mW/cm^2, 50 J/cm^2) using an ML7710 laser system [110]. This increase in survival was notably accompanied by a significant depletion of Tregs from ∼15% in the untreated control to <5% in the F(ab′)$_2$-PIT treatment group of the unilateral tumor model. Promising clinical studies are now being considered for clinical evaluation for CD25-targeted PIT in HNSCC and CSCC as a monotherapy and combination therapy with an immune checkpoint inhibitor (NCT05220748) [106].

Cancer-associated fibroblasts

Other important targets of PIT are CAFs—fibroblasts that are perpetually present in the TME. There is ongoing research regarding the role CAFs play in tumor progression, with many reporting that CAFs promote the development of Tregs, recruit MDSCs to the tumor site, and secrete the immunosuppressive cytokine TGF-β; others have observed CAF subpopulations that reduce tumor progression through the production of type I collagen which has been shown to mechanically restrain tumor spread [114]. CAF depletion has been successfully demonstrated through the use of a fibroblast activation protein (FAP)–specific single-chain variable fragment (scFv) conjugated to a ferritin PS carrier [115, 116]. While FAP is significantly overexpressed in >90% of epithelial cancer and has been proposed as a universal cancer marker, FAP expression is also non-negligible in normal tissues. In many instances, this precludes the administration of systemic anti-FAP therapies due to the high probability of side effects such as cachexia, bone toxicity, and death [115]. The use of the nanoparticle protein cage, apoferritin, as a zinc hexadecafluorophthalocyanine (ZnF16Pc) PS carrier under 671-nm laser irradiation (0.1 W/cm^2) significantly improves specificity, reducing off-target toxicity and allowing for greater penetration of solid tumors in comparison to small molecule drugs [115, 116]. More recent strategies take advantage of differential FAP expression as well, utilizing NIR-PIT to target CAFs or a combination of CAFs and cancer cells for maximal therapeutic effect in the treatment of esophageal cancers [117–119]. In these instances, NIR light was administrated to the cells with a red light-emitting diode with a power density of 15 or 25 mW/cm^2, as measured using an optical power meter [118]. Interestingly, dual-targeted CAF and cancer cell NIR-PIT significantly reduced tumor volume 24 days posttreatment following exposure to 670–710-nm light at 100 J/cm^2 [118]. In addition, a podoplanin-based NIR-PIT approach has been leveraged by Kato *et al*. [120]. Podoplanin (PDPN) is a transmembrane protein that is often expressed in cancer cells, lymphatic endothelial cells, and stromal cells such as CAFs. Kato *et al*. found that PDPN-targeted NIR-PIT significantly reduced tumor volume in PDPN-positive (MOC1) and PDPN-negative (MOC2) murine oral cancers, but only prolonged median survival from 20–30 days to 30–40 days in MOC1 cancers compared to control conditions following exposure to NIR light (690 nm, 150 mW/cm^2) at 50 J/cm^2 [120]. Although preclinical studies have demonstrated the efficacy of targeting CAF populations, CAF-targeted PIT is still challenging due to the diversity of CAF populations present in the TME and the contrasting tumor-restraining and tumor-promoting roles [121].

Myeloid-derived suppressor cells

While MDSCs are less commonly targeted than Tregs or CAFs, MDSC depletion has also been achieved with NIR-PIT. MDSCs are CD11b- and Gr-1-expressing immunosuppressive cells originating from the myeloid lineage during hematopoiesis that exert their effect on the TME through inducible nitric oxide synthase and arginase-1 [122]. The two main subpopulations of MDSCs are polymorphonuclear or neutrophilic (PMN)-MDSCs and monocytic (M)-MDSCs [123]. PMN-MDSCs are more commonly found in circulation or in the TME; this subtype primarily responds to immune stimuli by antigen-specific T-cell tolerance. In contrast, M-MDSCs less frequently infiltrate the TME and respond in both antigen-specific and nonspecific manners. Given the significance of PMN-MDSCs in disease progression and patient prognosis, current NIR-PIT strategies predominantly target this cell population [124]. Kato *et al*. demonstrated the use of an anti-Ly6G monoclonal antibody and IR700 to target PMN-MDSCs in mice [124]. Four mouse models were created with mEERL-hEGFR, MOC2-luc, and MOC1 lines representing PMN-MDSC-rich tumors and MC-38 representing an M-MDSC-rich tumor. Within each of the models, mice treated with Ly6G NIR-PIT showed a significant improvement in survival compared to untargeted NIR-PIT, and PMN-MDSC-rich models experienced greater prolonged survival compared to the M-MDSC-rich model. Interestingly, the Ly6G therapy was found to be specific to PMN-MDSCs alone, depleting PMN-MDSCs in a NIR light-dose-dependent manner (1, 5, 15, and 50 J) and exhibiting no cytotoxicity against cancer cells nor toward the M-MDSC subpopulation [124]. Ultimately, while more research is required to fully realize the capabilities of NIR-PIT in targeting MDSCs in the TME, this initial study presents promising results for the use of PICs in highly specific treatment regimes.

Tumor-associated macrophages

Another target whose investigation is still in its infancy is the TAMs. TAMs are macrophages that infiltrate the tumor stroma; macrophages are one of the most abundant immune cells in the TME [125]. They may develop into two subtypes during polarization: M1 macrophages (which play a pro-inflammatory role and are correlated with improved responses to therapy) and M2 macrophages (which participate in an anti-inflammatory and pro-tumoral response and are associated with poor prognosis). M2 TAMs have been found to overexpress CD206, a "pattern-recognition receptor" involved in the inhibition of the

pro-inflammatory cytokine IL-2. However, efforts to systemically deplete M2 TAMs and enhance the antitumor immune response have resulted in the widespread suppression of all M2 macrophages, which play important regulatory roles in noncancerous tissue [126]. As such, PIT has been proposed as a directed therapy option that would limit off-target effects. Hayashi *et al.* proposed the use of mannose-conjugated chlorin (M-chlorin) irradiated at 13.9 J/cm^2 (with an intensity of 30.8 mW/cm^2) at a wavelength of 660 nm to target TAMs present in gastric and colon cancer mouse models [127]. While no analysis of long-term survival was conducted in this study, Hayashi *et al.* determined that treatment by M-chlorin strongly suppressed tumor growth *in vivo* and significantly reduced the number of CD206$^+$ cells present in the tumors, as compared to treatment by other PSs, such as glucose-conjugated chlorin (G-chlorin) or chlorin alone [127]. More recent efforts have suggested the role of SIGLEC10$^+$ macrophages (a cell surface receptor of the sialic acid–binding immunoglobulin-like lectin family, often found on immune cells) in driving cancer progression and suppressing immune responses [128]. There have been efforts to deplete these TAMs through the use of photosensitizing nanocarriers targeting SIGLEC-10 after 5 h of incubation of sialic acid–modified zinc phthalocyanine derivative at a concentration of 0.5 μM at 3, 6, and 9 J/cm^2, though more research must be conducted regarding the *in vivo* benefits of this novel formulation [129].

Applications of photoimmunotherapy in cancer treatment regimens

Cancer cells deploy various mechanisms to resist treatments and evade immune surveillance that allow them to completely overthrow the homeostasis of the host. Some examples of this are downregulation of immune presenting proteins, upregulation of multidrug-resistant efflux transporters, and a carefully crafted immunosuppressive and physically stiff tumor microenvironment [28]; however, this is only a fraction of the many "alternative survival pathways" that cancer cells have at their disposal [50]. As such, it is becoming increasingly clear that the most effective therapies for cancer will require combination treatments that target multiple non-overlapping pathways while simultaneously decreasing offsite toxicity [50, 130]. FOLFIRINOX, for example, is currently the most used treatment for unresectable pancreatic cancer (and in some instances colon cancer), and it is composed of four separate drugs that each act on different molecular pathways [131]. PICs, due to their specific, customizable, disruptive, and cytotoxic effects, have also gained popularity in combination treatments, particularly involving chemotherapy, immunotherapy, and tumor resection.

PIT + chemotherapy

Chemotherapies are currently the gold-standard treatment for unresectable cancers, with >1 million people in the USA receiving some form of chemotherapy per year [132]. Their usefulness comes in their potency to attack critical components of actively dividing cells, which can lead to effective killing. Unfortunately, many cancer types have developed phenotypes that confer treatment resistance to chemotherapeutic drugs. Another issue with chemotherapeutics is the severe systemic side effects, such as fatigue, anemia, and a weakened immune system. However, with the combination of PICs, these side effects can be significantly reduced while simultaneously increasing cancer cell killing. There are a few mechanisms proposed for this synergy between PDT and chemotherapy. The first, as highlighted by Huang *et al.*, is that activating PSs (specifically BPD) leads to a decrease in ATP-binding cassette G2 (ABCG2) expression. ABCG2 is an efflux transporter that utilizes ATP binding and hydrolysis to pump drugs out of the cells, which has shown a direct correlation with chemoresistance in certain cancers [133]. Additionally, PDT disrupts redox homeostasis, which impairs metabolism and other cellular processes; this weakening likely makes cells more susceptible to a whole host of treatments, including but not limited to chemotherapy drugs [131]. This results in a lower concentration of chemotherapy drug needed, which also decreases offsite toxicity and side effects. As shown by Broekgaarden *et al.*, a sublethal neoadjuvant PDT dose of only 10 J/cm^2 decreased the IC_{50} for oxaliplatin in pancreatic cancer organoids 25-fold [131].

PIT, unlike PDT, has the additional benefit of targeted drug delivery. This efficiency varies based on the cell type and PIC formulation. In one formulation, Liang and colleagues created a PIC nanoliposome construct for simultaneous targeted delivery of BPD and irinotecan [130]. The targeting was done via cetuximab on the surface of the construct, and this resulted in a significant 2–6-fold increase in uptake between EGFR-positive and EGFR-negative cells; this, crucially, would further diminish the systemic toxicities of chemotherapy if this finding was consistent in humans [130]. Importantly, nanoliposomal conjugation with irinotecan and BPD was also 20% more cytotoxic than PIT and irinotecan in separate doses, which shows the impact of specific chemotherapy delivery. Furthermore, the combination index (a quantity used to measure synergism between therapies) for this treatment combination was 0.54, which shows that PIT and chemotherapy are synergistic rather than additive [130]. In another paper by Li *et al.*, IR700 PIT targeting MRP-1 (an ABC protein) combined with liposomal doxorubicin (Doxil) was tested on a small-cell lung cancer model [134]. PIT and Doxil, in a mixed 2D cell culture model, displayed significantly greater cytotoxicity than any monotherapy, with a combination index ranging from 0.113 to 0.547 [134]. One reason for this synergy is the aforementioned SUPR effect, whereby PITs impact on vasculature, stroma, and membrane integrity leads to a stark increase in drug delivery and persistence [71]. This is further exemplified by a 9-fold increase in Doxil accumulation *in vivo* in bilateral tumors following PIT administration [134].

PIT + immunotherapy

Immunotherapy has proven to be an incredible field in cancer medicine, particularly in the past decade with clinical approval of several immune checkpoint blockade (ICB) therapies, and has prolonged the survival of patients with many subtypes of aggressive cancer [135]. However, there are certain characteristics of cancer cells that inhibit ICB efficacy. Cancer cells often have low neoantigen load and downregulate MHC-I expression, factors essential in mounting robust antitumor immune responses, allowing them to escape immune surveillance [136]. Even if the immune system is boosted through various ICB therapies, these features make it difficult to mount a sustained immune response without antigen recognition [136]. This is likely why ICB therapy is only effective against a small subset of cancers. In pancreatic cancer, for example, ICB therapy is only effective in cancers presenting high microsatellite instability and thus greater neoantigen load; unfortunately, this only amounts to 1%–2% of diagnoses [137]. PIT can help improve immune surveillance by specifically killing the cancer cells via necrosis and apoptosis, which releases damage associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs) that can be recognized by antigen-presenting cells [138]. This reaction in turn leads to the activation of CD8 and CD4 cells characterized by CD107 and IFN

gamma expression that can recognize the tumor cells, effectively restoring immune surveillance capacity [138]. In short, PIT can make T cells more receptive to ICB therapy, which forms the basis for this combination treatment whose popularity is expanding in the current scientific landscape [136]. An ongoing phase Ib/II open-label study (NCT04305795) combining EGFR-targeted PIT (ASP1929) with anti-PD-1 therapy has shown promising preliminary results. The objective response rate in this study was 29.4% (5 out of 17 patients), with 3 patients showing complete response (17.6%). In addition, CD25-targeted PIT for HNSCC and CSCC in combination therapy with anti-PD1 (NCT05220748) is also being explored clinically.

Several preclinical studies have been performed to evaluate the combination of PIT with ICB therapy. In 2019, Nagaya *et al.* showed that CD44 (a cancer stem cell marker) targeted PIT and anti-PD1 ICB therapy was effective against several cancer lines *in vivo* [101]. Combination of CD44-targeted PIT with PD-1 blockade led to complete rejection in a majority of MC38 tumors (colon cancer), and significant survival increases were seen in lung and oral cancer models *in vivo* [101]. Additionally, combination treatment increased the intratumoral density of $CD8^+$, $CD11c^+MHCII^+$, and $CD11b^+$ cells suggesting increased activation of antigen-presenting cells and cytotoxic T cells. Furthermore, it was demonstrated via IFN gamma secretion that PIT induced antigen-specific T-cell responses to the MC38 antigens [101]. These observations appear to validate the DAMP and TAA generation model presented earlier, which serves to restore immunogenicity [101, 138]. This effect was not limited to the site of treatment alone but had an abscopal effect [138]. This resulted in 12 out of 15 mice treated with PIT and anti-PD1 completely rejecting bilateral tumors, despite only one side of the mouse being treated with PIT. Despite the effectiveness of PIT and anti-PD1 against MC38 colon cancer cells, it did not cause rejection of tumors in Lewis lung carcinoma (LLC) or mouse oral cancer (MOC1) orthotopic models. However, in a follow-up study, the ICB antibody was changed from anti-PD-1 to anti-CTLA4, which led to a decreased response against MC38 tumors, yet complete remission in 44% of MOC1 tumors *in vivo* [100]. Whereas PD-1 is a marker that inhibits the activity and proliferation of T cells, CTLA4 is most strongly associated with the recruitment of regulatory T cells [139]. In both instances, though, CD44-targeted PIT enhanced the efficacy of the ICB therapy, suggesting regulation of pathways upstream of the function of these immune modulating agents [100]. In supporting the previous studies' claims about the immune-stimulating effects of PIT, the combination of ICB and PIT has been shown to inhibit the catalysis of tryptophan to kynurenine, which leads to a decrease in regulatory T cells in colon and breast cancer models [140, 141]. These examples highlight another crucial benefit of combination therapy, namely, that the PIT targeting moiety, PS, and the ICB agent can be personalized to deal with the specific treatment-resistant modalities of different cancers.

PIT + resection

Resection is a balancing game, where cutting too little tumor can lead to recurrence and cutting too much can compromise esthetics and function. Additionally, many tumors form micrometastases—or new cancerous niches, away from the bulk tumor—such that completely removing the cancer in one excision remains exceptionally challenging [24, 142]. To help with these issues, PSs have been used previously as fluorescent agents, due to their limited quantum yields of fluorescence, for assisting in fluorescence image guidance during surgery [143]. PIT can therefore be used to aid in tumor resection in both neoadjuvant and adjuvant settings [142, 144, 145]. As a neoadjuvant, PIT can be used to induce necrosis and shrink tumor margins, thus making tumors eligible for surgical resections [144]. Alternatively, as an adjuvant treatment, PIT in the wound bed, post-surgery, can be used to specifically target cancer cells and elicit immunogenic cell death, thus removing any additional tumor or micrometastases [24, 142]. This effect has even been shown in particularly sensitive environments, such as brain tumors [145]. In a study by Moore *et al.*, an EGFR targeting IR700 PIC was tested for PIT efficacy in partial resection mice models of SCCHN tumors [142]. For both 50% and 90% partial tumor resection groups, PIT significantly inhibited tumor growth. In fact, the tumor growth was delayed more in the 50% partial tumor resection group in combination with PIT as compared to the 90% partial tumor resection group without PIT [142]. This displays the utility of PIT as an adjuvant treatment. Studies are now being conducted to evaluate the performance of PICs using multimodal imaging for guiding tumor resection surgeries followed by PIT to improve treatment outcomes in oral cancers [146, 147]. In addition, PICs have also been proposed for fluorescence molecular tomography (FMT) for noninvasive imaging of tumor cells. As an example, FMT on CD133-targeted PICs in glioblastoma was able to localize and quantify $CD133^+$ glioblastoma cells in live mice [99]. The use of FMT for diagnostic imaging of glioblastoma is hindered in humans due to the thickness of the skull, but FMT on CD133 could be applied in intraoperative imaging [99]. PICs are furthermore being proposed as a promising optical diagnostic imaging tool for other cancers, such as thyroid cancer [148].

Future perspectives and conclusions

Photoimmunotherapy has gained widespread attention due to its adaptability and versatility for targeting different cancer types and different cells in the tumor microenvironment. Unlike ADCs, where the chemotherapeutic agents are typically specific to a particular cancer type, PIT with a single antibody (anti-EGFR, among others) has been demonstrated to be effective against a variety of cancer types. Although PIT was first introduced nearly 40 years ago, its clinical potential is only now being realized with a recent clinical approval of PIT in Japan for head and neck cancers and several ongoing clinical trials. This progress in PIT can be attributed to significant advancements in irradiation technologies and rapid developments in the field of antibody engineering and conjugation chemistries. The development of new humanized antibodies and nanobodies with minimal toxicity, along with innovative conjugation techniques, has played a key role in overcoming challenges related to infusion reactions associated with chimeric antibodies such as cetuximab.

While PDT and PIT are not yet considered first-line therapies for treating advanced-stage tumors, they have been demonstrated to be ideal for use in both adjuvant and neoadjuvant settings. Future strategies should focus on designing rational combination therapies involving PIT targeted to either different targets on cancer cells to address receptor heterogeneity [149] or to different cells within the tumor microenvironment to enhance therapeutic outcomes (Table 2). This approach can be particularly advantageous for PIT, as it has been shown to overcome treatment resistance and resensitize resistant cells to chemotherapeutic agents. This allows for a therapeutic response even at lower doses, making the treatment more tolerable while still maintaining its efficacy. In addition, rational combination therapies should be considered as an option for future exploration. For example, PIT can lead to

Table 2. List of a few selected PIT targets and their treatment outcomes

	Target	Photosensitizer	Antibody/peptide	Combination treatment	Tumor type	PDT parameters (light dose)	Treatment outcome	Reference
Tumor microenvironment	CAFs	ZnF16Pc	FAP-specific single-chain variable fragment (scFv)	None	4T1 syngeneic breast cancer model	270 J/cm^2 @ 671 nm, single PIT or 2 PIT sessions	Double PIT increased survival as compared to single PIT	[115]
		IR700	Anti-EGFR (panitumumab), anti-HER2 (trastuzumab), or anti-FAP antibody	Combination PIT of CAFs and tumor cells	TE-4 and TE-8 esophageal tumor xenograft model	50 J/cm^2 @ 670–710 nm on days 1 and 2, 8 and 9. APC injection being performed on day 0	Dual-targeted PIT using Tra-IR700 and FAP-IR700 or Pan-IR700 and FAP-IR700 significantly suppressed tumor growth	[118]
		IR700	Anti-PDPN antibody	None	MOC1 and MOC2 syngeneic oral cancer model and MC38 syngeneic colon cancer model	50 J/cm^2 @ 690 nm on days 0 or days 0 and 1. APC injected on day −1	Double PIT inhibited tumor growth in MOC1 tumor model. Single NIR-PIT inhibited tumor growth in MC38 tumor model. MOC2 tumors were nonresponsive to single NIR-PIT	[120]
		IR700	Anti-FAP antibody	None	TE-4 esophageal tumor xenograft and TE-4/CAF tumor xenograft models	30 J/cm^2 @ 690 nm on days 0 and 3. APC injected on day −1	FAP-targeted NIR-PIT was inhibited tumor growth in heterotypic TE-4/CAF tumors while TE-4 xenografts were not responsive	[117]
		IR700	Anti-FAP antibody	5-Fluorouracil (5-FU) (chemotherapy)	TE-4 esophageal tumor xenograft and TE-4/CAF tumor xenograft models	3 cycles of 100 J/cm^2 @ 690 nm on days 1 and 2. APC injected on day 0	5-FU and NIR-PIT suppressed tumor growth suggesting elimination of CAFs improves 5-FU sensitivity leading to tumor suppression	[119]
	Tregs	IR700	Anti-CD25-F(ab′)$_2$	None	LL/2 syngeneic Lewis lung carcinoma model	100 J/cm^2 @ 690 nm	PIT significantly prolonged survival as compared to untreated mice	[108]
		IR700	Anti-CTLA4, anti-EGFR (panitumumab)	Combination PIT of Tregs and tumor cells	mEERL syngeneic oropharyngeal tumor model	50 J/cm^2 @ 690 nm	Dual-targeted NIR-PIT to EGFR and CTLA4 significantly suppressed tumor growth and prolonged survival	[103]
		IR700	Anti-CD25-IgG- or anti-CD25-F(ab′)$_2$	None	MC38 syngeneic colon cancer model	50 J/cm^2 @ 690 nm	Anti-CD25-F(ab′) had a significantly longer survival compared to anti-CD25-IgG-PIT	[110]
		IR700	Anti-CD25 and anti-CD44	Combination PIT of Tregs and cancer stem cells	MC38 syngeneic colon cancer model MOC1 syngeneic oral cancer model and LL/2 syngeneic Lewis lung carcinoma model	100 J/cm^2 @ 670–710 nm	Combined NIR-PIT showed significant tumor growth inhibition and prolonged survival compared with CD44-targeted NIR-PIT alone in all tumor models and showed prolonged survival compared with CD25-targeted NIR-PIT alone in MC38-luc and LL/2 tumors	[102]
		IR700	Anti-CD25-F(ab′)$_2$ and anti-EGFR (panitumumab)	Combination PIT of Tregs and cancer cells	mEERL syngeneic oropharyngeal tumor model	50 J/cm^2 @ 690 nm	Combined PIT group showed the greatest inhibition of tumor growth	[150]
	MDSCs	IR700	Anti-Ly6G	None	mEERL syngeneic oropharyngeal tumor model, MC38 syngeneic colon cancer model, MOC1 and MOC2 syngeneic oral cancer model	50 J/cm^2 @ 690 nm	Tumor growth was significantly inhibited in the NIR-PIT group for all models. Survival was significantly improved in mEERL, MOC1, and MOC2 tumors but not the MC38 tumors due to low MDSCs	[124]

(Continued)

Table 2. Continued

	Target	Photosensitizer	Antibody/peptide	Combination treatment	Tumor type	PDT parameters (light dose)	Treatment outcome	Reference
Tumor compartment	Cancer cells	IR700	Anti-mesothelin	None	A431/H9 tumor xenograft model	50 J/cm^2 on day 1 and 100 J/cm^2 on day 2. APC injected on day 0	Significantly prolonged survival observed in the NIR-PIT treatment group	[151]
		IR700	Anti-TROP2	None	PK-59 pancreatic tumor xenograft and TFK-1 cholangiocarcinoma tumor xenograft models	30 J/cm^2 on day 1 and 50 J/cm^2 on day 2 @ 690 nm. APC injected on day 0	Tumor volumes of PK-59 and TFK-1 tumors were significantly reduced compared to the untreated control group	[152]
		IR700	Anti-CD133	None	Patient-derived NCH421k (GBM-SC) tumor xenograft and U251 glioma xenograft models	100 J/cm^2 @690–710 nm for subcutaneous tumors. 50 J/cm^2 on day 1 and 100 J/cm^2 (@690–710 nm) on day 3 nm for orthotopic tumors. APC injected on day 0 for orthotopic tumors	Significant tumor regression PIT of subcutaneous tumors. Significant increase in survival for NIR-PIT treated orthotopic tumors	[99]
		IR700	Anti-EGFR (panitumumab)	None	A431 tumor xenograft model	30 J/cm^2	Significant increase in survival of mice treated with PIT	[39]
		IR700	Trastuzumab	None	SBC-3 tumor xenograft model	50 J/cm^2 on day 0 and 100 J/cm^2 on day 1. APC injected on day −1	PIT was effective in both SBC-3 tumors and cisplatin-resistant SBC-3/CDDP tumors with NIR-PIT being more effective (not statistically significant) on the SBC-3/CDDP tumors, as compared to SBC-3 tumors	[93]
	Cancer stem cells	IR700	Anti-CD44	Anti-PD1	MC38 syngeneic colon cancer model, MOC1 syngeneic oral cancer model, and LLC syngeneic lung cancer model	50 J/cm^2 on day 5 and 100 J/cm^2 on day 6. APC injected on day 4	Complete response in 70% MC38 tumor-bearing mice and 8% each in MOC1 and LLC tumor-bearing mice treated with combination therapy Complete response in 80% MC38 tumor-bearing mice with one or multiple untreated tumors treated with combination therapy	[101]
		IR700	Anti-CD44	Anti-CTLA4	MC38 syngeneic colon cancer model, MOC1 syngeneic oral cancer model, and LL/2 syngeneic lung cancer model	50 J/cm^2 on day 0 and 100 J/cm^2 on day 1. APC injected on day −1	Combination treatment marginally improved survival compared to the anti-CTLA4 monotherapy group in MC38 tumor-bearing mice. Combination treatment had a similar effect on survival as the NIR-PIT monotherapy group in LL/2-bearing mice. Combination treatment significantly improved survival as compared to the monotherapy groups in MOC1 tumor-bearing mice	[100]
		IR700	Anti-CD44	Anti-PD1	MOC2 syngeneic oral cancer model	50 J/cm^2 @690 nm on day 1. APC injected on day 0	Complete remission in 66.7% mice as which was significantly better than survival for monotherapy groups	[153]
		IR700	Anti-CD44	None	MOC1 and MOC2 syngeneic oral cancer models	50 J/cm^2 on day 0 and 100 J/cm^2 on day 1 for unilateral model. APC injected on day −1. 100 J/cm^2 only to the right-sided tumor on day 1. APC injected on day 0	Significantly prolonged survival in the NIR-PIT treatment group in MOC1 and MOC2 unilateral and bilateral tumor-bearing mice	[154]

the subsequent overexpression of other targets that may provide a survival advantage or resistance to treatment. PDT induces hypoxia, leading to the overexpression of vascular endothelial growth factor (VEGF) and its cognate receptor (VEGFR), promoting vascularization, survival, and metastasis [155]. PIT with a combination of tumor cell and VEGFR targeting provides a potential alternative and should be explored further [156].

To conclude, PIT as a therapeutic modality holds a major advantage of specificity over conventional PDT and traditional cancer treatments. Current clinical trials exploring the efficacy of NIR-PIT in cutaneous and head-and-neck squamous cell carcinoma should provide extensive clinical data supporting its safety and efficacy across these tumor types. As of current, there are several drawbacks associated with PIT. Firstly, PIT relies on the use of antibodies that specifically target cancer cells or other specific cell types in the tumor microenvironment; for some tumor types, suitable targeting antibodies are not well developed or available, limiting the application of PIT to those cancers. In addition, direct illumination for tumors that are accessible, such as those on the skin or in the head and neck region, is being currently explored, whereas for tumors located deep within the body or in less accessible areas, delivering the necessary light can be challenging. Additionally, the penetration of NIR light through tissue is no more than 5 mm, so it is not possible to completely irradiate large tumors [157]. The effectiveness of PIT can also be influenced by the tumor microenvironment, including factors such as hypoxia (low oxygen levels) and the presence of dense stromal tissue, which can further impede light penetration and reduce the efficacy of the therapy.

Due to these factors, PIT is currently being explored more cautiously, primarily in tumor types where there is a clear potential for clinical success. As the technology and understanding of PIT continue to evolve, it may become more feasible to apply it to a broader range of cancers.

Author contributions

Derek Allen (Conceptualization [supporting], Writing—original draft [equal], Writing—review & editing [equal]), Madeline Szoo (Conceptualization [supporting], Writing—original draft [equal], Writing—review & editing [equal]), Tessa van Bergen (Conceptualization [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Ani Seppelin (Writing—original draft [supporting], Writing—review & editing [supporting]), Jeonghyun Oh (Writing—original draft [supporting], Writing—review & editing [supporting]), and Mohammad Saad (Conceptualization-Lead, Supervision-Lead, Writing—original draft [equal], Writing—review & editing [equal]).

Conflict of interest

M.A.S. is an instructor in Dermatology at Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School. D.A. is a research technician at the Wellman Center for Photomedicine, Massachusetts General Hospital. M.J.S., A.S., and J.O. are undergraduate students at Northeastern University. T.D.v.B. was a visiting scholar at Wellman Center for Photomedicine, Massachusetts General Hospital.

Funding

The authors would like to acknowledge funding from the Dana-Farber/Harvard Cancer Center and University of Massachusetts U54 Partnership (U54CA156732) to M.A.S. M.J.S. and J.O. were supported by the Northeastern University CaNCURE Program funded by the National Cancer Institute (NCI) Grant (R25CA174650). A.S. was supported by the Dana-Farber/Harvard Cancer Center Young Empowered Scientists for ContinUed Research Engagement (YES for CURE) Program funded by the National Cancer Institute (NCI) Grant (R25CA221738).

References

1. Debela, DT, Muzazu, SG, Heraro, KD *et al.* New approaches and procedures for cancer treatment: current perspectives. *SAGE Open Medicine* 2021;**9**:20503121211034366. https://doi.org/10.1177/20503121211034366.
2. De Silva, P, Saad, MA, Thomsen, HC *et al.* Photodynamic therapy, priming and optical imaging: potential co-conspirators in treatment design and optimization — a Thomas Dougherty Award for Excellence in PDT paper. *Journal of Porphyrins and Phthalocyanines* 2020;**24**:1320–60. https://doi.org/10.1142/S1088424620300098.
3. Celli, JP, Spring, BQ, Rizvi, I *et al.* Imaging and photodynamic therapy: mechanisms, monitoring, and optimization. *Chem Rev* 2010;**110**:2795–838. https://doi.org/10.1021/cr900300p.
4. Viana Cabral, F, Quilez Alburquerque, J, Roberts, HJ *et al.* Shedding light on chemoresistance: the perspective of photodynamic therapy in cancer management. *Int J Mol Sci* 2024;**25**:3811. https://doi.org/10.3390/ijms25073811.
5. Ramia, P, Bodgi, L, Mahmoud, D *et al.* Radiation-induced fibrosis in patients with head and neck cancer: a review of pathogenesis and clinical outcomes. *Clin Med Insights Oncol* 2022;**16**:11795549211036898. https://doi.org/10.1177/11795549211036898.
6. Straub, JM, New, J, Hamilton, CD *et al.* Radiation-induced fibrosis: mechanisms and implications for therapy. *J Cancer Res Clin Oncol* 2015;**141**:1985–94. https://doi.org/10.1007/s00432-015-1974-6.
7. Siddiqui, SA, Siddiqui, S, Hussain, MAB *et al.* Clinical evaluation of a mobile, low-cost system for fluorescence guided photodynamic therapy of early oral cancer in India. *Photodiagnosis Photodyn Ther* 2022;**38**:102843. https://doi.org/10.1016/j.pdpdt.2022.102843.
8. Hendren, SK, Hahn, SM, Spitz, FR *et al.* Phase II trial of debulking surgery and photodynamic therapy for disseminated intraperitoneal tumors. *Ann Surg Oncol* 2001;**8**:65–71. https://doi.org/10.1007/s10434-001-0065-x.
9. Sindelar, WF, DeLaney, TF, Tochner, Z *et al.* Technique of photodynamic therapy for disseminated intraperitoneal malignant neoplasms: phase I study. *Arch Surg* 1991;**126**:318–24. https://doi.org/10.1001/archsurg.1991.01410270062011.
10. Delaney, TF, Sindelar, WF, Tochner, Z *et al.* Phase I study of debulking surgery and photodynamic therapy for disseminated intraperitoneal tumors. *Int J Radiat Oncol Biol Phys* 1993;**25**:445–57. https://doi.org/10.1016/0360-3016(93)90066-5.
11. Bown, SG, Rogowska, AZ, Whitelaw, DE *et al.* Photodynamic therapy for cancer of the pancreas. *Gut* 2002;**50**:549–57. https://doi.org/10.1136/gut.50.4.549.
12. Zhao, Z, Ukidve, A, Kim, J *et al.* Targeting strategies for tissue-specific drug delivery. *Cell* 2020;**181**:151–67. https://doi.org/10.1016/j.cell.2020.02.001.
13. Xenaki, KT, Oliveira, S, van Bergen en Henegouwen, PMP. Antibody or antibody fragments: implications for molecular imaging and targeted therapy of solid tumors. *Front Immunol* 2017;**8**:1–6. https://doi.org/10.3389/fimmu.2017.01287.

14. Kataoka, H, Nishie, H, Tanaka, M *et al.* Potential of photodynamic therapy based on sugar-conjugated photosensitizers. *J Clin Med* 2021;**10**:841. https://doi.org/10.3390/jcm10040841.
15. Steichen, SD, Caldorera-Moore, M, Peppas, NA. A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. *Eur J Pharm Sci* 2013;**48**:416–27. https://doi.org/10.1016/j.ejps.2012.12.006.
16. Iyer, KA, Ivanov, J, Tenchov, R *et al.* Emerging targets and therapeutics in immuno-oncology: insights from landscape analysis. *J Med Chem* 2024;**67**:8519-44. https://doi.org/10.1021/acs.jmedchem.4c00568.
17. Colombo, R, Rich, JR. The therapeutic window of antibody drug conjugates: a dogma in need of revision. *Cancer Cell* 2022;**40**:1255–63. https://doi.org/10.1016/j.ccell.2022.09.016.
18. Fu, Z, Li, S, Han, S *et al.* Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther* 2022;**7**:93. https://doi.org/10.1038/s41392-022-00947-7.
19. Shen, L, Sun, X, Chen, Z *et al.* ADCdb: the database of antibody–drug conjugates. *Nucleic Acids Res* 2023;**52**:D1097–109.
20. Beck, A, Goetsch, L, Dumontet, C *et al.* Strategies and challenges for the next generation of antibody-drug conjugates. *Nat Rev Drug Discov* 2017;**16**:315–37. https://doi.org/10.1038/nrd.2016.268.
21. Abdolvahab, MH, Karimi, P, Mohajeri, N *et al.* Targeted drug delivery using nanobodies to deliver effective molecules to breast cancer cells: the most attractive application of nanobodies. *Cancer Cell Int* 2024;**24**:67. https://doi.org/10.1186/s12935-024-03259-8.
22. Alsaab, HO, Alharbi, FD, Alhibs, AS *et al.* PLGA-based nanomedicine: history of advancement and development in clinical applications of multiple diseases. *Pharmaceutics* 2022;**14**:1–30. https://doi.org/10.3390/pharmaceutics14122728.
23. Mew, D, Wat, CK, Towers, GH *et al.* Photoimmunotherapy: treatment of animal tumors with tumor-specific monoclonal antibody-hematoporphyrin conjugates. *J Immunol* 1983;**130**:1473–7. https://doi.org/10.4049/jimmunol.130.3.1473.
24. Spring, BQ, Abu-Yousif, AO, Palanisami, A *et al.* Selective treatment and monitoring of disseminated cancer micrometastases in vivo using dual-function, activatable immunoconjugates. *Proc Natl Acad Sci U S A* 2014;**111**:E933–42. https://doi.org/10.1073/pnas.1319493111.
25. Huang, H-C, Pigula, M, Fang, Y *et al.* Immobilization of photoimmunoconjugates on nanoparticles leads to enhanced light-activated biological effects. *Small* 2018;**14**:1800236. https://doi.org/10.1002/smll.201800236.
26. Castano, AP, Mroz, P, Hamblin, MR. Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer* 2006;**6**:535–45. https://doi.org/10.1038/nrc1894.
27. Bhandari, C, Moffat, A, Shah, N *et al.* PD-L1 immune checkpoint targeted photoactivable liposomes (iTPALs) prime the stroma of pancreatic tumors and promote self-delivery. *Adv Healthc Mater* 2024;**13**:e2304340.
28. Obaid, G, Celli, JP, Broekgaarden, M *et al.* Engineering photodynamics for treatment, priming and imaging. *Nat Rev Bioeng* 2024;**2**:752–69. https://doi.org/10.1038/s44222-024-00196-z.
29. Pogue, BW, O'Hara, JA, Demidenko, E *et al.* Photodynamic therapy with verteporfin in the radiation-induced fibrosarcoma-1 tumor causes enhanced radiation sensitivity. *Cancer Res* 2003;**63**:1025–33.
30. Garg, AD, Agostinis, P. ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. *Photochem Photobiol Sci* 2014;**13**:474–87. https://doi.org/10.1039/c3pp50333j.
31. Kessel, D. Photodynamic therapy: critical PDT theory. *Photochem Photobiol* 2023;**99**:199–203. https://doi.org/10.1111/php.13616.
32. Kessel, D, Oleinick, NL. Cell death pathways associated with photodynamic therapy: an update. *Photochem Photobiol* 2018;**94**:213–8. https://doi.org/10.1111/php.12857.
33. Saad, MA, Hasan, T. Spotlight on photoactivatable liposomes beyond drug delivery: an enabler of multitargeting of molecular pathways. *Bioconjug Chem* 2022;**33**:2041–64. https://doi.org/10.1021/acs.bioconjchem.2c00376.
34. Coates, PJ, Lorimore, SA, Wright, EG. Damaging and protective cell signalling in the untargeted effects of ionizing radiation. *Mutat Res* 2004;**568**:5–20. https://doi.org/10.1016/j.mrfmmm.2004.06.042.
35. Sorrin, AJ, Kemal Ruhi, M, Ferlic, NA *et al.* Photodynamic therapy and the biophysics of the tumor microenvironment. *Photochem Photobiol* 2020;**96**:232–59. https://doi.org/10.1111/php.13209.
36. Quílez-Alburquerque, J, Saad, MA, Descalzo, AB *et al.* Hyaluronic acid-poly(lactic-co-glycolic acid) nanoparticles with a ruthenium photosensitizer cargo for photokilling of oral cancer cells. *J Photochem Photobiol A Chem* 2023;**436**:114349. https://doi.org/10.1016/j.jphotochem.2022.114349.
37. Obaid, G, Bano, S, Mallidi, S *et al.* Impacting pancreatic cancer therapy in heterotypic in vitro organoids and in vivo tumors with specificity-tuned, NIR-activable photoimmunonanoconjugates: towards conquering desmoplasia? *Nano Lett* 2019;**19**:7573–87. https://doi.org/10.1021/acs.nanolett.9b00859.
38. Sato, K, Ando, K, Okuyama, S *et al.* Photoinduced ligand release from a silicon phthalocyanine dye conjugated with monoclonal antibodies: a mechanism of cancer cell cytotoxicity after near-infrared photoimmunotherapy. *ACS Central Science* 2018;**4**:1559–69. https://doi.org/10.1021/acscentsci.8b00565.
39. Mitsunaga, M, Ogawa, M, Kosaka, N *et al.* Cancer cell–selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules. *Nat Med* 2011;**17**:1685–91. https://doi.org/10.1038/nm.2554.
40. Maruoka, Y, Wakiyama, H, Choyke, PL *et al.* Near infrared photoimmunotherapy for cancers: a translational perspective. *EBioMedicine* 2021;**70**:103501. https://doi.org/10.1016/j.ebiom.2021.103501.
41. Nakajima, K, Ogawa, M. Near-infrared photoimmunotherapy and anti-cancer immunity. *Int Immunol* 2023;**36**:57–64. https://doi.org/10.1093/intimm/dxad042.
42. Sano, K, Nakajima, T, Choyke, PL *et al.* Markedly enhanced permeability and retention effects induced by photoimmunotherapy of tumors. *ACS Nano* 2013;**7**:717–24. https://doi.org/10.1021/nn305011p.
43. Snyder, JW, Greco, WR, Bellnier, DA *et al.* Photodynamic therapy: a means to enhanced drug delivery to tumors. *Cancer Res* 2003;**63**:8126–31.
44. Obaid, G, Bano, S, Thomsen, H *et al.* Remediating desmoplasia with EGFR-targeted photoactivable multi-inhibitor liposomes doubles overall survival in pancreatic cancer. *Adv Sci* 2022;**9**:2104594.
45. Overchuk, M, Harmatys, KM, Sindhwani, S *et al.* Subtherapeutic photodynamic treatment facilitates tumor nanomedicine delivery and overcomes desmoplasia. *Nano Lett* 2021;**21**:344–52. https://doi.org/10.1021/acs.nanolett.0c03731.
46. Bhandari, C, Moffat, A, Fakhry, J *et al.* A single photodynamic priming protocol augments delivery of α-PD-L1 mAbs and

induces immunogenic cell death in head and neck tumors. *Photochem Photobiol* 2023;**100**:1647–58. https://doi.org/10.1111/php.13865.
47. Roh, JS, Sohn, DH. Damage-associated molecular patterns in inflammatory diseases. *Immune Netw* 2018;**18**:1–14. https://doi.org/10.4110/in.2018.18.e27.
48. Mallidi, S, Anbil, S, Bulin, A-L *et al.* Beyond the barriers of light penetration: strategies, perspectives and possibilities for photodynamic therapy. *Theranostics* 2016;**6**:2458–87. https://doi.org/10.7150/thno.16183.
49. Weijer, R, Clavier, S, Zaal, EA *et al.* Multi-OMIC profiling of survival and metabolic signaling networks in cells subjected to photodynamic therapy. *Cell Mol Life Sci* 2017;**74**:1133–51. https://doi.org/10.1007/s00018-016-2401-0.
50. Huang, H-C, Mallidi, S, Liu, J *et al.* Photodynamic therapy synergizes with irinotecan to overcome compensatory mechanisms and improve treatment outcomes in pancreatic cancer. *Cancer Res* 2016;**76**:1066–77. https://doi.org/10.1158/0008-5472.CAN-15-0391.
51. Saad, MA, Zhung, W, Stanley, ME *et al.* Photoimmunotherapy retains its anti-tumor efficacy with increasing stromal content in heterotypic pancreatic cancer spheroids. *Mol Pharm* 2022;**19**:2549–63. https://doi.org/10.1021/acs.molpharmaceut.2c00260.
52. Goff, BA, Bamberg, M, Hasan, T. Photoimmunotherapy of human ovarian carcinoma cells ex vivo. *Cancer Res* 1991;**51**:4762–7.
53. Goff, BA, Hermanto, U, Rumbaugh, J *et al.* Photoimmunotherapy and biodistribution with an OC125-chlorin immunoconjugate in an in vivo murine ovarian cancer model. *Br J Cancer* 1994;**70**:474–80. https://doi.org/10.1038/bjc.1994.330.
54. Hamblin, MR, Miller, JL, Hasan, T. Effect of charge on the interaction of site-specific photoimmunoconjugates with human ovarian cancer cells. *Cancer Res* 1996;**56**:5205–10.
55. Molpus, KL, Hamblin, MR, Rizvi, I *et al.* Intraperitoneal photoimmunotherapy of ovarian carcinoma xenografts in nude mice using charged photoimmunoconjugates. *Gynecol Oncol* 2000;**76**:397–404. https://doi.org/10.1006/gyno.1999.5705.
56. Hongrapipat, J, Kopečková, P, Liu, J *et al.* Combination chemotherapy and photodynamic therapy with fab′ fragment targeted HPMA copolymer conjugates in human ovarian carcinoma cells. *Mol Pharm* 2008;**5**:696–709. https://doi.org/10.1021/mp800006e.
57. Lu, ZR, Shiah, JG, Kopečková, P *et al.* Preparation and biological evaluation of polymerizable antibody fab′ fragment targeted polymeric drug delivery system. *J Control Release* 2001;**74**:263–8. https://doi.org/10.1016/S0168-3659(01)00332-7.
58. Shirasu, N, Shibaguchi, H, Yamada, H *et al.* Highly versatile cancer photoimmunotherapy using photosensitizer-conjugated avidin and biotin-conjugated targeting antibodies. *Cancer Cell Int* 2019;**19**:299. https://doi.org/10.1186/s12935-019-1034-4.
59. Hussain, AF, Kampmeier, F, von Felbert, V *et al.* SNAP-tag technology mediates site specific conjugation of antibody fragments with a photosensitizer and improves target specific phototoxicity in tumor cells. *Bioconjug Chem* 2011;**22**:2487–95. https://doi.org/10.1021/bc200304k.
60. Sandland, J, Boyle, RW. Photosensitizer antibody–drug conjugates: past, present, and future. *Bioconjug Chem* 2019;**30**:975–93. https://doi.org/10.1021/acs.bioconjchem.9b00055.
61. Sasso, JM, Tenchov, R, Bird, R *et al.* The evolving landscape of antibody–drug conjugates: in depth analysis of recent research progress. *Bioconjug Chem* 2023;**34**:1951–2000. https://doi.org/10.1021/acs.bioconjchem.3c00374.
62. Bryden, F, Maruani, A, Rodrigues, JMM *et al.* Assembly of high-potency photosensitizer–antibody conjugates through application of dendron multiplier technology. *Bioconjug Chem* 2018;**29**:176–81. https://doi.org/10.1021/acs.bioconjchem.7b00678.
63. Sadiki, A, Kercher, EM, Lu, H *et al.* Site-specific bioconjugation and convergent click chemistry enhances antibody–chromophore conjugate binding efficiency. *Photochem Photobiol* 2020;**96**:596–603. https://doi.org/10.1111/php.13231.
64. Savellano, MD, Hasan, T. Targeting cells that overexpress the epidermal growth factor receptor with polyethylene glycolated BPD verteporfin photosensitizer immunoconjugates. *Photochem Photobiol* 2003;**77**:431–9. https://doi.org/10.1562/0031-8655(2003)077<0431:TCTOTE>2.0.CO;2.
65. Savellano, MD, Hasan, T. Photochemical targeting of epidermal growth factor receptor: a mechanistic study. *Clin Cancer Res* 2005;**11**:1658–68. https://doi.org/10.1158/1078-0432.CCR-04-1902.
66. Nguyen, A, Bhandari, C, Keown, M *et al.* Increasing the dye payload of cetuximab-IRDye800CW enables photodynamic therapy. *Mol Pharm* 2024;**21**:3296–309. https://doi.org/10.1021/acs.molpharmaceut.4c00046.
67. Duska, LR, Hamblin, MR, Bamberg, MP *et al.* Biodistribution of charged F(ab')2 photoimmunoconjugates in a xenograft model of ovarian cancer. *Br J Cancer* 1997;**75**:837–44. https://doi.org/10.1038/bjc.1997.149.
68. Hamblin, MR, Governatore, MD, Rizvi, I *et al.* Biodistribution of charged 17.1A photoimmunoconjugates in a murine model of hepatic metastasis of colorectal cancer. *Br J Cancer* 2000;**83**:1544–51. https://doi.org/10.1054/bjoc.2000.1486.
69. St Denis, TG, Hamblin, MR. Synthesis, bioanalysis and biodistribution of photosensitizer conjugates for photodynamic therapy. *Bioanalysis* 2013;**5**:1099–114. https://doi.org/10.4155/bio.13.37.
70. Nagaya, T, Nakamura, Y, Sato, K *et al.* Improved microdistribution of antibody-photon absorber conjugates after initial near infrared photoimmunotherapy (NIR-PIT). *J Control Release* 2016;**232**:1–8. https://doi.org/10.1016/j.jconrel.2016.04.003.
71. Kobayashi, H, Choyke, PL. Super enhanced permeability and retention (SUPR) effects in tumors following near infrared photoimmunotherapy. *Nanoscale* 2016;**8**:12504–9. https://doi.org/10.1039/C5NR05552K.
72. Paul, S, Konig, MF, Pardoll, DM *et al.* Cancer therapy with antibodies. *Nat Rev Cancer* 2024;**24**:399–426. https://doi.org/10.1038/s41568-024-00690-x.
73. del Carmen, MG, Rizvi, I, Chang, Y *et al.* Synergism of epidermal growth factor receptor–targeted immunotherapy with photodynamic treatment of ovarian cancer in vivo. *J Natl Cancer Inst* 2005;**97**:1516–24. https://doi.org/10.1093/jnci/dji314.
74. Wei, D, Qi, J, Hamblin, MR *et al.* Near-infrared photoimmunotherapy: design and potential applications for cancer treatment and beyond. *Theranostics* 2022;**12**:7108–31. https://doi.org/10.7150/thno.74820.
75. Peng, Z, Lv, X, Huang, S. Photoimmunotherapy: a new paradigm in solid tumor immunotherapy. *Cancer Control* 2022;**29**:10732748221088825. https://doi.org/10.1177/10732748221088825.
76. Mohiuddin, TM, Zhang, C, Sheng, W *et al.* Near infrared photoimmunotherapy: a review of recent progress and their target molecules for cancer therapy. *Int J Mol Sci* 2023;**24**:2655. https://doi.org/10.3390/ijms24032655.
77. Wang, S, Hüttmann, G, Zhang, Z *et al.* Light-controlled delivery of monoclonal antibodies for targeted photoinactivation of

Ki-67. *Mol Pharm* 2015;**12**:3272–81. https://doi.org/10.1021/acs.molpharmaceut.5b00260.
78. Grandis, JR, Melhem, MF, Gooding, WE *et al.* Levels of TGF-α and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst* 1998;**90**:824–32. https://doi.org/10.1093/jnci/90.11.824.
79. Kohler, M, Bauknecht, T, Grimm, M *et al.* Epidermal growth factor receptor and transforming growth factor alpha expression in human ovarian carcinomas. *Eur J Cancer* 1992;**28**:1432–7. https://doi.org/10.1016/0959-8049(92)90538-D.
80. Røtterud, R, Nesland, JM, Berner, A *et al.* Expression of the epidermal growth factor receptor family in normal and malignant urothelium. *BJU Int* 2005;**95**:1344–50. https://doi.org/10.1111/j.1464-410X.2005.05497.x.
81. Levantini, E, Maroni, G, Del Re, M *et al.* EGFR signaling pathway as therapeutic target in human cancers. *Semin Cancer Biol* 2022;**85**:253–75. https://doi.org/10.1016/j.semcancer.2022.04.002.
82. Cai, W-Q, Zeng, L-S, Wang, L-F *et al.* The latest battles between EGFR monoclonal antibodies and resistant tumor cells. *Front Oncol* 2020;**10**:1–16. https://doi.org/10.3389/fonc.2020.01249.
83. Yu, J, Fang, T, Yun, C *et al.* Antibody-drug conjugates targeting the human epidermal growth factor receptor family in cancers. *Front Mol Biosci* 2022;**9**:1–11. https://doi.org/10.3389/fmolb.2022.847835.
84. Cognetti, DM, Johnson, JM, Curry, JM *et al.* Phase 1/2a, open-label, multicenter study of RM-1929 photoimmunotherapy in patients with locoregional, recurrent head and neck squamous cell carcinoma. *Head Neck* 2021;**43**:3875–87. https://doi.org/10.1002/hed.26885.
85. Drugs, S.C.o.N. *Report on the Deliberation Results Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau*. Ministry of Health, Labour and Welfare, 2020.
86. von Felbert, V, Bauerschlag, D, Maass, N *et al.* A specific photoimmunotheranostics agent to detect and eliminate skin cancer cells expressing EGFR. *J Cancer Res Clin Oncol* 2016;**142**:1003–11. https://doi.org/10.1007/s00432-016-2122-7.
87. Jin, J, Barnett, JD, Mironchik, Y *et al.* Photoimmunotheranostics of epithelioid sarcoma by targeting CD44 or EGFR. *Transl Oncol* 2024;**45**:101966. https://doi.org/10.1016/j.tranon.2024.101966.
88. Inagaki, FF, Wakiyama, H, Furusawa, A *et al.* Near-infrared photoimmunotherapy (NIR-PIT) of bone metastases. *Biomed Pharmacother* 2023;**160**:114390. https://doi.org/10.1016/j.biopha.2023.114390.
89. Siddiqui, MR, Railkar, R, Sanford, T *et al.* Targeting epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) expressing bladder cancer using combination photoimmunotherapy (PIT). *Sci Rep* 2019;**9**:2084. https://doi.org/10.1038/s41598-019-38575-x.
90. Nagaya, T, Okuyama, S, Ogata, F *et al.* Near infrared photoimmunotherapy using a fiber optic diffuser for treating peritoneal gastric cancer dissemination. *Gastric Cancer* 2019;**22**:463–72. https://doi.org/10.1007/s10120-018-0871-5.
91. Sato, K, Nagaya, T, Mitsunaga, M *et al.* Near infrared photoimmunotherapy for lung metastases. *Cancer Lett* 2015;**365**:112–21. https://doi.org/10.1016/j.canlet.2015.05.018.
92. Hirata, H, Kuwatani, M, Nakajima, K *et al.* Near-infrared photoimmunotherapy (NIR-PIT) on cholangiocarcinoma using a novel catheter device with light emitting diodes. *Cancer Sci* 2021;**112**:828–38. https://doi.org/10.1111/cas.14780.
93. Takahashi, K, Taki, S, Yasui, H *et al.* HER2 targeting near-infrared photoimmunotherapy for a CDDP-resistant small-cell lung cancer. *Cancer Med* 2021;**10**:8808–19. https://doi.org/10.1002/cam4.4381.
94. Kim, KS, Kim, J, Kim, DH *et al.* Multifunctional trastuzumab–chlorin e6 conjugate for the treatment of HER2-positive human breast cancer. *Biomater Sci* 2018;**6**:1217–26. https://doi.org/10.1039/C7BM01084B.
95. Korsak, B, Almeida, GM, Rocha, S *et al.* Porphyrin modified trastuzumab improves efficacy of HER2 targeted photodynamic therapy of gastric cancer. *Int J Cancer* 2017;**141**:1478–89. https://doi.org/10.1002/ijc.30844.
96. Donin, NM, Reiter, RE. Why targeting PSMA is a game changer in the management of prostate cancer. *J Nucl Med* 2018;**59**:177–82. https://doi.org/10.2967/jnumed.117.191874.
97. Nagaya, T, Nakamura, Y, Okuyama, S *et al.* Near-infrared photoimmunotherapy targeting prostate cancer with prostate-specific membrane antigen (PSMA) antibody. *Mol Cancer Res* 2017;**15**:1153–62. https://doi.org/10.1158/1541-7786.MCR-17-0164.
98. Lathia, J, Liu, H, Matei, D. The clinical impact of cancer stem cells. *Oncologist* 2019;**25**:123–31. https://doi.org/10.1634/theoncologist.2019-0517.
99. Jing, H, Weidensteiner, C, Reichardt, W *et al.* Imaging and selective elimination of glioblastoma stem cells with theranostic near-infrared-labeled CD133-specific antibodies. *Theranostics* 2016;**6**:862–74. https://doi.org/10.7150/thno.12890.
100. Maruoka, Y, Furusawa, A, Okada, R *et al.* Near-infrared photoimmunotherapy combined with CTLA4 checkpoint blockade in syngeneic mouse cancer models. *Vaccines (Basel)* 2020;**8**:1–14. https://doi.org/10.3390/vaccines8030528.
101. Nagaya, T, Friedman, J, Maruoka, Y *et al.* Host immunity following near-infrared photoimmunotherapy is enhanced with PD-1 checkpoint blockade to eradicate established antigenic tumors. *Cancer Immunol Res* 2019;**7**:401–13. https://doi.org/10.1158/2326-6066.CIR-18-0546.
102. Maruoka, Y, Furusawa, A, Okada, R *et al.* Combined CD44- and CD25-targeted near-infrared photoimmunotherapy selectively kills cancer and regulatory T cells in syngeneic mouse cancer models. *Cancer Immunol Res* 2020;**8**:345–55. https://doi.org/10.1158/2326-6066.CIR-19-0517.
103. Kato, T, Okada, R, Furusawa, A *et al.* Simultaneously combined cancer cell- and CTLA4-targeted NIR-PIT causes a synergistic treatment effect in syngeneic mouse models. *Mol Cancer Ther* 2021;**20**:2262–73. https://doi.org/10.1158/1535-7163.MCT-21-0470.
104. Furusawa, A, Okada, R, Inagaki, F *et al.* CD29 targeted near-infrared photoimmunotherapy (NIR-PIT) in the treatment of a pigmented melanoma model. *Onco Targets Ther* 2022;**11**:2019922. https://doi.org/10.1080/2162402X.2021.2019922.
105. Gillenwater, AM, Cognetti, D, Johnson, JM *et al.* RM-1929 photoimmunotherapy in patients with recurrent head and neck cancer: results of a multicenter phase 2a open-label clinical trial. *J Clin Oncol* 2018;**36**:6039–9. https://doi.org/10.1200/JCO.2018.36.15_suppl.6039.
106. Cognetti, DM, Curry, JM, KuklÃk, R *et al.* A phase 1, first-in-human, drug dose-escalation study of RM-1995 photoimmunotherapy, as monotherapy or combined with pembrolizumab, in patients with advanced cutaneous squamous cell carcinoma or with head and neck squamous cell carcinoma. *J Clin Oncol* 2022;**40**:TPS6103-TPS6103. https://doi.org/10.1200/JCO.2022.40.16_suppl.TPS6103.
107. Jang, J-E, Hajdu, CH, Liot, C *et al.* Crosstalk between regulatory T cells and tumor-associated dendritic cells negates

anti-tumor immunity in pancreatic cancer. *Cell Rep* 2017;**20**:558–71. https://doi.org/10.1016/j.celrep.2017.06.062.
108. Sato, K, Sato, N, Xu, B *et al.* Spatially selective depletion of tumor-associated regulatory T cells with near-infrared photoimmunotherapy. *Sci Transl Med* 2016;**8**:352ra110-352ra110. https://doi.org/10.1126/scitranslmed.aaf6843.
109. Leao, IC, Ganesan, P, Armstrong, TD *et al.* Effective depletion of regulatory T cells allows the recruitment of mesothelin-specific CD8+ T cells to the antitumor immune response against a mesothelin-expressing mouse pancreatic adenocarcinoma. *Clin Transl Sci* 2008;**1**:228–39. https://doi.org/10.1111/j.1752-8062.2008.00070.x.
110. Okada, R, Maruoka, Y, Furusawa, A *et al.* The effect of antibody fragments on CD25 targeted regulatory T cell near-infrared photoimmunotherapy. *Bioconjug Chem* 2019;**30**:2624–33. https://doi.org/10.1021/acs.bioconjchem.9b00547.
111. Eiting, MM, Clark, JE, Astor, T *et al.* Safety and efficacy of basiliximab for immunosuppression holiday in lung transplant patients. *J Heart Lung Transplant* 2021;**40**:S376. https://doi.org/10.1016/j.healun.2021.01.1059.
112. Kappos, L, Wiendl, H, Selmaj, K *et al.* Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015;**373**:1418–28. https://doi.org/10.1056/NEJMoa1501481.
113. Gold, R, Giovannoni, G, Selmaj, K *et al.* Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;**381**:2167–75. https://doi.org/10.1016/S0140-6736(12)62190-4.
114. Guo, T, Xu, J. Cancer-associated fibroblasts: a versatile mediator in tumor progression, metastasis, and targeted therapy. *Cancer Metastasis Rev* 2024;**43**:1095–116. https://doi.org/10.1007/s10555-024-10186-7.
115. Zhen, Z, Tang, W, Wang, M *et al.* Protein nanocage mediated fibroblast-activation protein targeted photoimmunotherapy to enhance cytotoxic T cell infiltration and tumor control. *Nano Lett* 2017;**17**:862–9. https://doi.org/10.1021/acs.nanolett.6b04150.
116. Li, L, Zhou, S, Lv, N *et al.* Photosensitizer-encapsulated ferritins mediate photodynamic therapy against cancer-associated fibroblasts and improve tumor accumulation of nanoparticles. *Mol Pharm* 2018;**15**:3595–9. https://doi.org/10.1021/acs.molpharmaceut.8b00419.
117. Watanabe, S, Noma, K, Ohara, T *et al.* Photoimmunotherapy for cancer-associated fibroblasts targeting fibroblast activation protein in human esophageal squamous cell carcinoma. *Cancer Biol Ther* 2019;**20**:1234–48. https://doi.org/10.1080/15384047.2019.1617566.
118. Sato, H, Noma, K, Ohara, T *et al.* Dual-targeted near-infrared photoimmunotherapy for esophageal cancer and cancer-associated fibroblasts in the tumor microenvironment. *Sci Rep* 2022;**12**:20152. https://doi.org/10.1038/s41598-022-24313-3.
119. Katsube, R, Noma, K, Ohara, T *et al.* Fibroblast activation protein targeted near infrared photoimmunotherapy (NIR PIT) overcomes therapeutic resistance in human esophageal cancer. *Sci Rep* 2021;**11**:1693. https://doi.org/10.1038/s41598-021-81465-4.
120. Kato, T, Furusawa, A, Okada, R *et al.* Near-infrared photoimmunotherapy targeting podoplanin-expressing cancer cells and cancer-associated fibroblasts. *Mol Cancer Ther* 2023;**22**:75–88. https://doi.org/10.1158/1535-7163.MCT-22-0313.
121. Zhang, T, Ren, Y, Yang, P *et al.* Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma. *Cell Death Dis* 2022;**13**:897. https://doi.org/10.1038/s41419-022-05351-1.
122. Lasser, SA, Ozbay Kurt, FG, Arkhypov, I *et al.* Myeloid-derived suppressor cells in cancer and cancer therapy. *Nat Rev Clin Oncol* 2024;**21**:147–64. https://doi.org/10.1038/s41571-023-00846-y.
123. Zhou, J, Nefedova, Y, Lei, A *et al.* Neutrophils and PMN-MDSC: their biological role and interaction with stromal cells. *Semin Immunol* 2018;**35**:19–28. https://doi.org/10.1016/j.smim.2017.12.004.
124. Kato, T, Fukushima, H, Furusawa, A *et al.* Selective depletion of polymorphonuclear myeloid derived suppressor cells in tumor beds with near infrared photoimmunotherapy enhances host immune response. *Onco Targets Ther* 2022;**11**:2152248. https://doi.org/10.1080/2162402X.2022.2152248.
125. Pittet, MJ, Michielin, O, Migliorini, D. Clinical relevance of tumour-associated macrophages. *Nat Rev Clin Oncol* 2022;**19**:402–21. https://doi.org/10.1038/s41571-022-00620-6.
126. Wang, S, Wang, J, Chen, Z *et al.* Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. *npj Precision Oncology* 2024;**8**:31. https://doi.org/10.1038/s41698-024-00522-z.
127. Hayashi, N, Kataoka, H, Yano, S *et al.* A novel photodynamic therapy targeting cancer cells and tumor-associated macrophages. *Mol Cancer Ther* 2015;**14**:452–60. https://doi.org/10.1158/1535-7163.MCT-14-0348.
128. Guo, Y, Ke, S, Xie, F *et al.* SIGLEC10+ macrophages drive gastric cancer progression by suppressing CD8+ T cell function. *Cancer Immunol Immunother* 2023;**72**:3229–42. https://doi.org/10.1007/s00262-023-03488-2.
129. Almeida-Marrero, V, Bethlehem, F, Longo, S *et al.* Tailored multivalent targeting of Siglecs with photosensitizing liposome nanocarriers. *Angew Chem Int Ed Engl* 2022;**61**:e202206900. https://doi.org/10.1002/anie.202206900.
130. Liang, BJ, Pigula, M, Baglo, Y *et al.* Breaking the selectivity-uptake trade-off of photoimmunoconjugates with nanoliposomal irinotecan for synergistic multi-tier cancer targeting. *J Nanobiotechnol* 2020;**18**:1. https://doi.org/10.1186/s12951-019-0560-5.
131. Broekgaarden, M, Rizvi, I, Bulin, AL *et al.* Neoadjuvant photodynamic therapy augments immediate and prolonged oxaliplatin efficacy in metastatic pancreatic cancer organoids. *Oncotarget* 2018;**9**:13009–22. https://doi.org/10.18632/oncotarget.24425.
132. Halpern, MT, Yabroff, KR. Prevalence of outpatient cancer treatment in the United States: estimates from the Medical Panel Expenditures Survey (MEPS). *Cancer Invest* 2008;**26**:647–51. https://doi.org/10.1080/07357900801905519.
133. König, J, Hartel, M, Nies, AT *et al.* Expression and localization of human multidrug resistance protein (ABCC) family members in pancreatic carcinoma. *Int J Cancer* 2005;**115**:359–67. https://doi.org/10.1002/ijc.20831.
134. Li, F, Mao, C, Yeh, S *et al.* Combinatory therapy of MRP1-targeted photoimmunotherapy and liposomal doxorubicin promotes the antitumor effect for chemoresistant small cell lung cancer. *Int J Pharm* 2022;**625**:122076. https://doi.org/10.1016/j.ijpharm.2022.122076.
135. Waldman, AD, Fritz, JM, Lenardo, MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol* 2020;**20**:651–68. https://doi.org/10.1038/s41577-020-0306-5.
136. Wu, X, Li, T, Jiang, R *et al.* Targeting MHC-I molecules for cancer: function, mechanism, and therapeutic prospects. *Mol Cancer* 2023;**22**:194. https://doi.org/10.1186/s12943-023-01899-4.

137. Coston, T, Desai, A, Babiker, H *et al.* Efficacy of immune checkpoint inhibition and cytotoxic chemotherapy in mismatch repair-deficient and microsatellite instability-high pancreatic cancer: Mayo Clinic experience. *JCO Precis Oncol* 2023;**7**:e2200706. https://doi.org/10.1200/PO.22.00706.
138. De Silva, P, Bano, S, Pogue, BW *et al.* Photodynamic priming with triple-receptor targeted nanoconjugates that trigger T cell-mediated immune responses in a 3D in vitro heterocellular model of pancreatic cancer. *Nanophotonics* 2021;**10**:3199–214. https://doi.org/10.1515/nanoph-2021-0304.
139. Pardoll, DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;**12**:252–64. https://doi.org/10.1038/nrc3239.
140. Zhang, N, Sun, Q, Li, J *et al.* A lipid/PLGA nanocomplex to reshape tumor immune microenvironment for colon cancer therapy. *Regen Biomater* 2024;**11**:rbae036. https://doi.org/10.1093/rb/rbae036.
141. Wu, C, Xu, J, Xie, Z *et al.* Light-responsive hyaluronic acid nanomicelles co-loaded with an IDO inhibitor focus targeted photoimmunotherapy against "immune cold" cancer. *Biomater Sci* 2021;**9**:8019–31. https://doi.org/10.1039/D1BM01409A.
142. Moore, LS, de Boer, E, Warram, JM *et al.* Photoimmunotherapy of residual disease after incomplete surgical resection in head and neck cancer models. *Cancer Med* 2016;**5**:1526–34. https://doi.org/10.1002/cam4.752.
143. McCracken, DJ, Schupper, AJ, Lakomkin, N *et al.* Turning on the light for brain tumor surgery: a 5-aminolevulinic acid story. *Neuro Oncol* 2022;**24**:S52–61. https://doi.org/10.1093/neuonc/noac191.
144. Huggett, MT, Jermyn, M, Gillams, A *et al.* Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. *Br J Cancer* 2014;**110**:1698–704. https://doi.org/10.1038/bjc.2014.95.
145. Mączyńska, J, Raes, F, Da Pieve, C *et al.* Triggering anti-GBM immune response with EGFR-mediated photoimmunotherapy. *BMC Med* 2022;**20**:16. https://doi.org/10.1186/s12916-021-02213-z.
146. Saad, MA, Grimaldo-Garcia, S, Sweeney, A *et al.* Dual-function antibody conjugate-enabled photoimmunotherapy complements fluorescence and photoacoustic imaging of head and neck cancer spheroids. *Bioconjug Chem* 2024;**35**:51–63. https://doi.org/10.1021/acs.bioconjchem.3c00406.
147. Saad, MA, Xavierselvan, M, Sharif, HA *et al.* Dual function antibody conjugates for multimodal imaging and photoimmunotherapy of cancer cells. *Photochem Photobiol* 2022;**98**:220–31. https://doi.org/10.1111/php.13501.
148. Shao, C, Li, Z, Zhang, C *et al.* Optical diagnostic imaging and therapy for thyroid cancer. *Materials Today Bio* 2022;**17**:100441. https://doi.org/10.1016/j.mtbio.2022.100441.
149. Nakajima, T, Sano, K, Choyke, PL *et al.* Improving the efficacy of photoimmunotherapy (PIT) using a cocktail of antibody conjugates in a multiple antigen tumor model. *Theranostics* 2013;**3**:357–65. https://doi.org/10.7150/thno.5908.
150. Okada, R, Furusawa, A, Vermeer, DW *et al.* Near-infrared photoimmunotherapy targeting human-EGFR in a mouse tumor model simulating current and future clinical trials. *EBioMedicine* 2021;**67**:103345. https://doi.org/10.1016/j.ebiom.2021.103345.
151. Nagaya, T, Nakamura, Y, Sato, K *et al.* Near infrared photoimmunotherapy with an anti-mesothelin antibody. *Oncotarget* 2016;**7**:23361–9. https://doi.org/10.18632/oncotarget.8025.
152. Nishimura, T, Mitsunaga, M, Sawada, R *et al.* Photoimmunotherapy targeting biliary-pancreatic cancer with humanized anti-TROP2 antibody. *Cancer Med* 2019;**8**:7781–92. https://doi.org/10.1002/cam4.2658.
153. Wakiyama, H, Furusawa, A, Okada, R *et al.* Increased immunogenicity of a minimally immunogenic tumor after cancer-targeting near infrared photoimmunotherapy. *Cancers (Basel)* 2020;**12**:3747. https://doi.org/10.3390/cancers12123747.
154. Nagaya, T, Nakamura, Y, Okuyama, S *et al.* Syngeneic mouse models of oral cancer are effectively targeted by anti–CD44-based NIR-PIT. *Mol Cancer Res* 2017;**15**:1667–77. https://doi.org/10.1158/1541-7786.MCR-17-0333.
155. Ferrario, A, von Tiehl, KF, Rucker, N *et al.* Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma. *Cancer Res* 2000;**60**:4066–9.
156. Mashayekhi, V, Xenaki, KT, van Bergen en Henegouwen, PMP *et al.* Dual targeting of endothelial and cancer cells potentiates in vitro nanobody-targeted photodynamic therapy. *Cancers (Basel)* 2020;**12**:2732. https://doi.org/10.3390/cancers12102732.
157. Padalkar, MV, Pleshko, N. Wavelength-dependent penetration depth of near infrared radiation into cartilage. *Analyst* 2015;**140**:2093–100. https://doi.org/10.1039/C4AN01987C.

© The Author(s) 2025. Published by Oxford University Press on behalf of Antibody Therapeutics. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Antibody Therapeutics, 2025, 8(1), 68–85
https://doi.org/10.1093/abt/tbaf001
Review Article