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Photodynamic therapy-based combinations with immunotherapy in colon cancer treatment

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01

General

Introduction

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Introduction

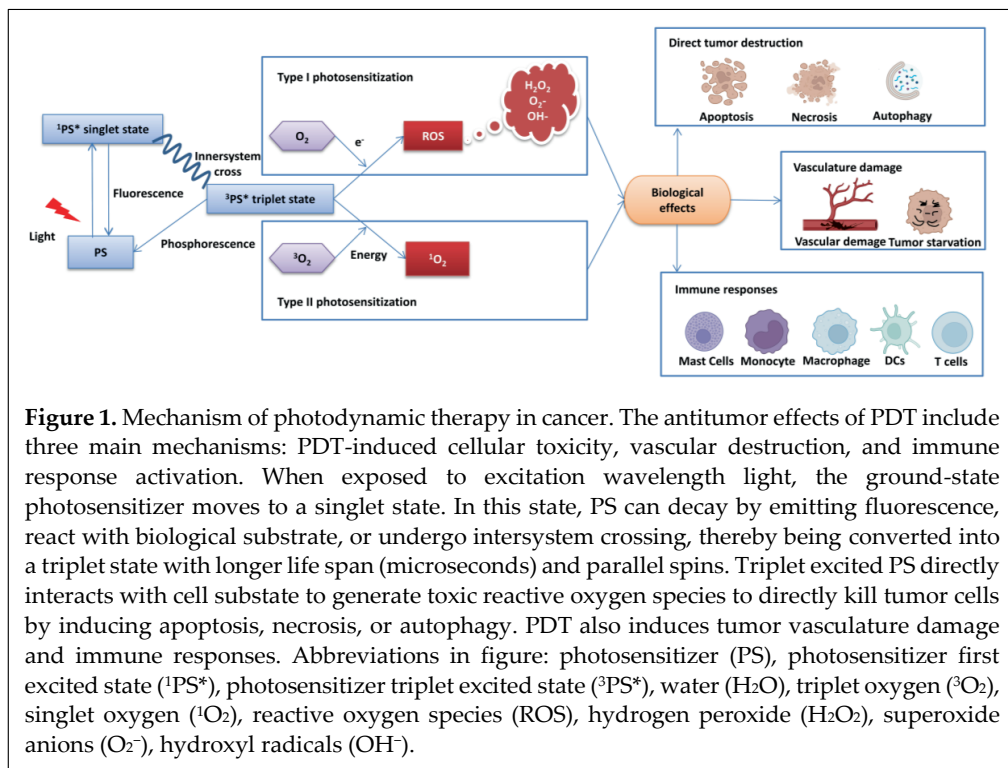
Photodynamic therapy was founded by the Danish physician Niels Finsen. He won the Nobel prize in 1903 “in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science” [1]. Although the term “photodynamic therapy (PDT)” was first coined by Von Tappeiner, who proposed the use of phototherapy for the regression of tumors and other diseases [2]. Both men were pioneers in photobiology, yet it took many years for phototherapy to achieve its clinical application. An important breakthrough was achieved by the discovery of the selectivity and phototoxicity of haematoporphyrin in tumors [3]. Importantly, in 1999 the U.S. Food and Drug Administration (FDA) approved the first PDT drug in Canada [4]. Since then, PDT has rapidly developed as a promising and powerful tool in the modern world of therapeutic regimens to combat cancer.

Photodynamic Therapy in Cancer Treatment

Mechanism of Photodynamic Therapy in Cancer

Initially, PDT was commonly used to treat nonmalignant diseases (acne and age-related macular degeneration) [5–7]. Since the mid-1950s, PDT has been explored as a treatment option in a large variety of preclinical cancer models; when increased specificity and selectivity were achieved in the early 1990s, clinical approval was obtained for cancer treatment [8]. For example, PDT is used to target lung tumors, esophageal cancer, gastric carcinoma, breast cancer, brain tumors, head and neck tumors, colorectal cancers, etc. [9]. PDT is a multistage process, based on three components: a photosensitizer (PS), a light source, and tumor oxygen. It exerts its tumor destruction effects through photochemical and photobiological mechanisms [10] (Figure 1). The PS has negligible cellular toxicity under a lack of light, regardless of the route of administration. An appropriate light dose can provide enough energy for the accumulated PS in the diseased tissue to move into an excited state from the ground state, leading to the production of free radicals and reactive oxygen species (ROS). Depending on the nature of this reaction, such photosensitized processes are defined as Type I and Type II. During the Type I process, triplet excited PS

directly interacts with the cell substrate to generate free radicals (e.g., hydroxyl radicals, superoxide anion, and hydrogen peroxide) through a hydrogen atom (electron) transfer. These radicals can further interact with oxygen to produce toxic reactive oxygen species. A Type II process, however, produces highly reactive singlet oxygen ($^1\text{O}_2$) via oxygen ($^3\text{O}_2$) through electron transfer. These reactive species are highly cytotoxic and directly kill tumor cells by inducing apoptosis, necrosis, or autophagy [11]. However, the kind of cell death induced by the PDT treatment depends on the characteristics of the PS (e.g., intracellular location and activation wavelength), cell type, and PDT dose (including PS concentration and total light fluence) [12]. Moreover, the destruction of tumor cells results in the production of new tumor-derived antigens and the increased expression of stress proteins. These PDT-killed tumor pieces are phagocytosed by macrophages and lead to acute inflammation, leukocyte infiltration, and maturation activation of dendritic cells [13]. PDT also reduces tumor volume indirectly by inducing microvascular shutdown and vessel leakage. This event can lead to nutrient starvation and hypoxia [14]. In general, the function of these mechanisms is cooperative, but which particular mechanism is dominant in PDT's tumor-controlling effects is still unclear and requires further study.



Generations of PS

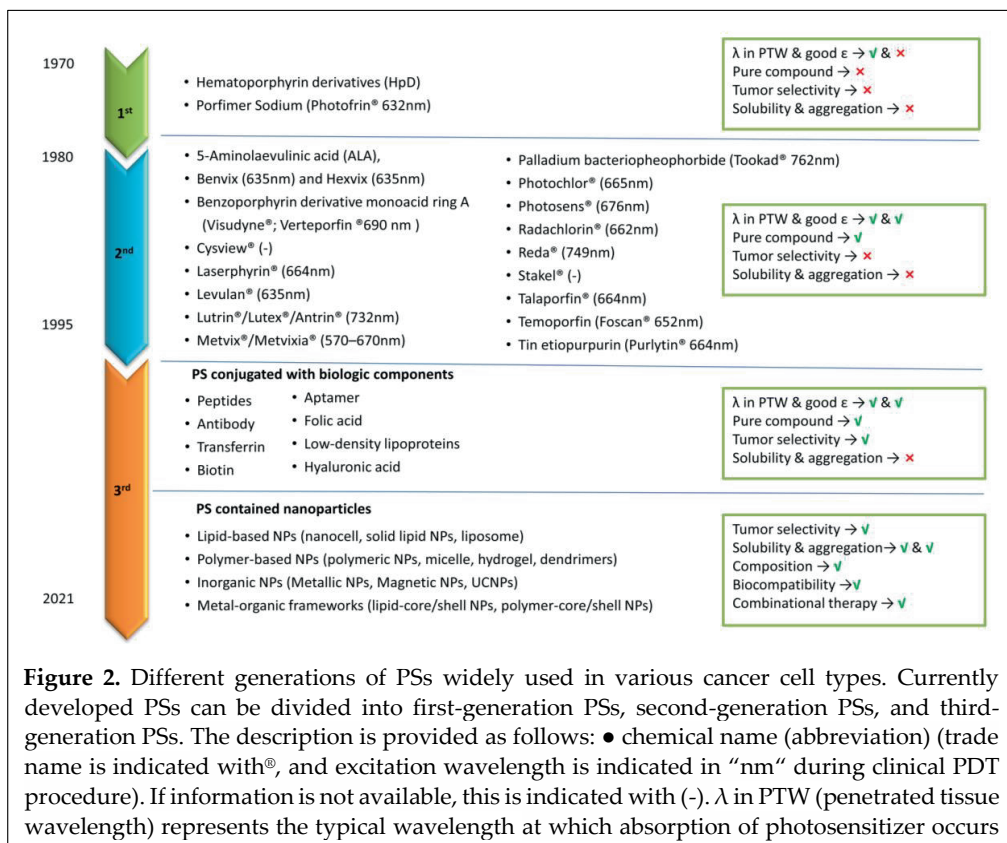
The advantages of PDT are its low systemic toxicity, its minimal invasiveness, and its targeting opportunities. The therapeutic efficacy of PDT depends on the properties of light, availability of sufficient tissue oxygen, and PS characteristics (uptake and

localization). However, further studies are needed for PDT to achieve a better therapeutic effect with fewer shortcomings. For example, a superficial irradiation approach for noninvasive PDT has the limitation of tumor tissue penetration. However, this can be improved by coupling PDT to optical fibers or intraluminal/interstitial settled multi light sources [15]. Moreover, hypoxia, the major barrier of PDT efficiency and the main reason for PDT resistance, can be counteracted by PS dosimetry [16–19]. In addition to the improvement of irradiation light equipment and optimization of oxygen ratio in the tumor, there is a need for further optimization of PSs. So far, PSs can be categorized into three generations [20]. First-generation PSs were developed in the 1970s and include hematoporphyrin derivatives (HpD) and its purified form, as well as Photofrin (trade name of porfimer sodium) [21] (Figure 2). Whereas certain anti-tumor effects of Photofrin have been reported for several types of cancer (brain, lung, skin, gastric, etc.) in clinical tests [22], some drawbacks (e.g., complex composition, weak absorption at 630 nm) and obvious side effects (light-dependent skin sensitivity caused by the high PS dose that is needed to achieve therapeutic effects) of first-generation PSs limited their clinical application [22–24]. These shortcomings triggered the development of second-generation PSs (Figure 2). The second generation was still based on porphyrin and chlorin structures, but their purity and synthesis were improved. Furthermore, second-generation PSs had a longer light activation wavelength and shorter half-life [25]. Examples include 5-aminolaevulinic acid (ALA), temoporfin (Foscan®), palladium bacteriopheophorbide (Tookad®), tin etiopurpurin (Purlytin®), and benzoporphyrin derivative monoacid ring A (BPD-MA; Visudyne®; Verteporfin®). 5-ALA is a key precursor to the synthesis of heme. On the basis of this characteristic, 5-ALA is used as a prodrug for PDT by producing PPIX (photosensitizer), the immediate precursor of heme. ALA derivatives such as methyl, benzyl, and hexyl ALA ester have also been approved for use in cancer diagnosis and treatment [26]. As we discussed in Section 2.1., PDT can impair vascular structures or induce microvascular stasis, depending on the PS type and protocols used. For example, vascular targeted PDT with BPD-MA (VP, Verteporfin®) can effectively induce endothelial cell injury to cause vascular damage [27]. Another example is Radachlorin®-mediated PDT. In a typical protocol, after 4 h intravenous injection of Radachlorin® into tumors, irradiation is provided at 100 mW/cm² for a total light dose of 20 J/cm² using a 662 nm laser. Five days after PDT treatment, intravital imaging revealed a disrupted tumor vasculature [28]. The major difference between the first- and second-generation PSs is the diffusion rate of the PDT-generated singlet oxygen and ROS caused by their subcellular uptake in organelles such as lysosomes, nuclear envelope, and mitochondria [29]. The diffusion rate of the PDT-generated ROS caused by the particular uptake of PSs leads to a difference in PDT sensitivity and PDT-induced cell death type, because of the short ROS half-life time [29,30]. PSs localized mitochondrially and in other organelles induced more ROS generation and induced significantly higher photodamage efficacy than PSs taken up by lysosomes [31].

Despite the improved therapeutic effect of second-generation PSs, the complex tumor microenvironment (especially PDT-enhanced degree of hypoxia) and the glutathione (GSH) depletion effects on ROS weaken the toxic efficiency of PDT-generated ROS [32]. Moreover, the hydrophilicity, tumor selectivity, and body clearance rate of PSs were far

from optimal. For example, Foscan®, which needs to be injected in a painful way in a polyethylene glycol, ethanol, and water mixture, demonstrated no significant difference in fluorescence between tumor tissue and its surrounding tissues in a rat breast cancer model [33]. Such challenges have endorsed research on the further optimization of PSs to the third generation of compounds [34] (Figure 2). The selectivity problem of PSs for tumor tissue over healthy tissue has been addressed by the covalent binding of PSs to ligands, such as folate, transferrin, peptides, and antibodies. Such PS conjugation enabled more selective recognition and internalization by tumor cells, thus minimizing damage to healthy cells. As certain receptor sites on tumor cell surfaces, such as biotin, androgen, and glucose receptors, are highly expressed on tumor cells, the conjugated targets for PSs enable more selectivity in cancer cell targeting [35].

An alternative approach for optimization would be to increase the efficiency and selectivity of the PS delivery system [36]. An emerging solution in this line comprises the use of nanoparticles (NPs; 1–100 nm). Owing to their enhanced permeability and retention (EPR) effect, as well as subcellular size, NPs have been shown to support PSs, in order to penetrate deeper into tissue and preferably accumulate in tumors [37]. These NPs can increase the PS stability, reduce its degradation before it accumulates in tumor cells, and improve the hydrophobic PS solubility by increasing its aggregation in an aqueous environment. Additionally, modifying the surface of the NP with targeting components also offers more opportunities for PSs to be delivered more specifically in diseased tissues [38]. As a result of enhanced PS delivery to tumor cells, a larger concentration is available to harness stronger PDT effects, without inducing excessive off-target systemic side effects [39,40].



Personalized PDT-based Cancer Combination Therapy in Clinical trails

As illustrated above, important for clinical approval has been that PDT is noninvasive and nontoxic, spatiotemporally selective. However, the therapeutic efficacy of PDT alone against several deep or hypoxic solid tumors is limited due to its inherent drawbacks and the clinical challenges (metastasis, recurrence, and resistance) of cancer therapy [41,42]. The mechanisms that contribute to PDT resistance might be changed in drug uptake and efflux rates of PSs, activation of abnormal cell signaling pathway activation, and hypoxia after PDT. However, two-thirds of the reports showed no cross-resistance to chemotherapy-, radiotherapy-, and hyperthermia-resistant cells in PDT-resistant cells [43]. From this perspective, by combining PDT with other current cancer modalities, one may be able to exploit the strengths and bypass the weaknesses of different therapies (Figure 3). As presented in the subsequent sections, this approach has great promise and can lead to additive (or even synergistic) therapeutic effects [44]. Consistent with this notion, PDT-combined strategies have gradually entered into clinical trials for the treatment of basal cell carcinoma, non-small-cell lung cancer, and other types of cancer. In particular, its combination with surgery, radiotherapy, and chemotherapy has been investigated (clinically trailed data was collected on 20th August 2021 from resource: <http://clinicaltrials.gov>; Table 1). Further efforts are needed to discover new PSs,

specifically for deeper located cancers, and to optimize PS-mediated PDT in various tumor types.

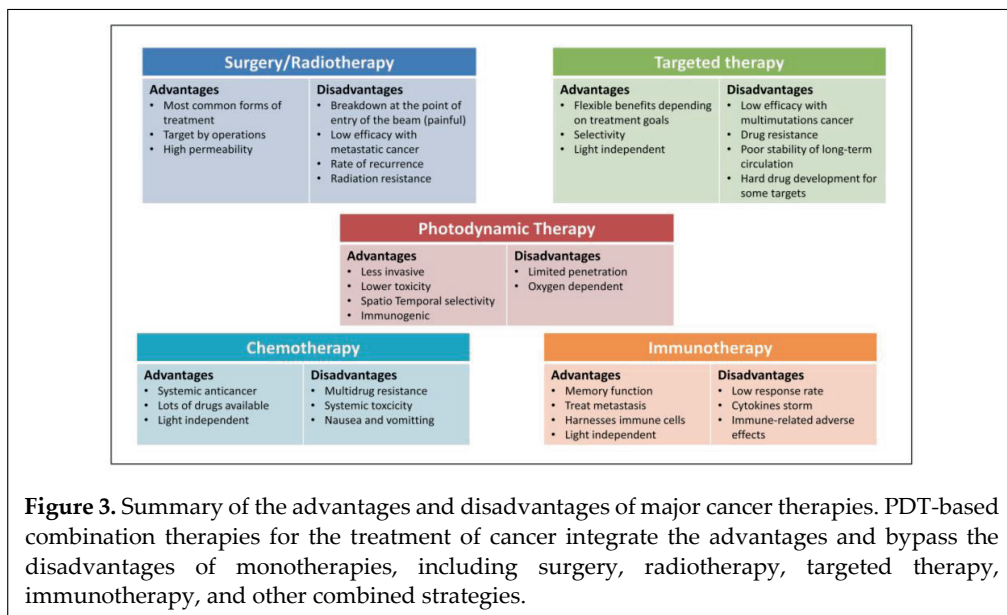


Table 1. Clinical trials of photodynamic therapy-based combination strategies.

Phase	Photosensitizer	Combined Interventions	Cancer Type	Status	Years of Study	Clinical Trial Reference Number
Phase I	Temoporfin (Foscan®)	Surgery	Non-small-cell lung cancer	Completed	2013–2019	NCT01854684
	HPPH (Photochlor®)	Surgery	Head and neck cancer	Completed	2007–2018	NCT00470496
	HPPH (Photochlor®)	Surgery (laser therapy)	Primary or invasive larynx cancer	Completed	2008–2018	NCT00675233
	Motexafin lutetium	Surgery	Cervical intraepithelial neoplasia	Terminated	2003–2013	NCT00005808
	- (Not marked)	Surgery and radiosensitizer (etanidazole)	Intraperitoneal or pleural cancer	Terminated	2003–2013	NCT00028782
	Porfimer sodium (Photofrin®)	Surgery	Malignant mesothelioma	Completed	2003–2011	NCT00054002
	Hematoporphyrin derivative	Radiotherapy (brachytherapy)	Lung cancer	Completed	2004–2013	NCT00014066

	Hexaminolevulinate (HAL)	Placebo ointment	Cervical intraepithelial neoplasia	Completed	2010–2016	NCT01256424
	Aminolaevulinic acid (ALA)	Adjuvant (vitamin D ₃)	Pre-malignant anal tumor	Recruiting	2016–	NCT02698293
	Porfimer sodium (Photofrin®)	Chemotherapy (gemcitabine hydrochloride)	Advanced pancreatic cancer	Completed	2013–2018	NCT01770132
Phase II	Aminolaevulinic acid (ALA)	Surgery	Superficial non-melanoma skin cancer	Completed	2003–2013	NCT00002963
	Porfimer sodium (Photofrin®)	Surgery and chemotherapy	Non-small-cell lung cancer	Terminated	2008–2020	NCT00601848
	Porfimer sodium (Photofrin®)	Surgery and chemotherapy (cisplatin)	Malignant pleural mesothelioma	Completed	2016–2018	NCT02662504
	Porfimer sodium (Photofrin®)	Surgery and chemotherapy	Malignant pleural mesothelioma	Recruiting	2014–	NCT02153229
	Hexaminolevulinate (HAL)	Placebo	Cervical intraepithelial neoplasia	Terminated	2008–2013	NCT00708942
	Aminolaevulinic acid (ALA)	Placebo	Cervical intraepithelial neoplasia	Completed	2015–2019	NCT02631863
Phase II/III	Methyl-5-aminolevulinic acid hydrochloride (Metvix®)	Surgery (Ablative CO ₂ laser)	Basal cell carcinoma	Completed	2010–2015	NCT01260987
Phase III	Porfimer sodium (Photofrin®)	Chemotherapy (gemcitabine/cisplatin)	Cholangiocarcinoma	Terminated	2014–2019	NCT02082522
	Porfimer sodium (Photofrin®)	Chemotherapy (S-1)	Cholangiocarcinoma	Completed	2009–2014	NCT00869635
	Methyl-5-aminolevulinic acid hydrochloride (Metvix®)	Placebo cream	Basal cell carcinoma	Completed	2007–2010	NCT00472108
	Methyl-5-aminolevulinic acid hydrochloride (Metvix®)	Cryotherapy	Basal cell carcinoma	Completed	2007–2010	NCT00469417

PDT Combined with Surgery

PDT has been frequently used in conjunction with surgery in clinical cancer trials (Table 1) due to the image-guided effect (NCT03638622) and increased anticancer therapeutic effect [45]. A phase I clinical trial (NCT00470496) of intraoperative PDT combined with surgery in the treatment of primary or recurrent head and neck cancer showed an improved cure rate, by allowing for larger tumor-free margins while preserving normal structures. A clinical study of surgical PDT underscored that there was no relapse (follow-up of 0.6–5 years) in basal cell carcinoma (BCC) patient tissues after combined treatment. Moreover, transmission electron microscopy analysis of tumor tissues indicated fewer side-effects in patients after treatment [46]. In addition, when PDT was combined with surgery, the tumoral depth showed less limitation in skin cancer patients. Post-surgical PDT improved not only the efficacy of tumor thickness reduction and the survival rate in both squamous cell carcinoma and basal cell carcinoma patients [47], but also the recovery rate and appearance satisfaction by reducing the excision range of the tumor lesions [48]. In addition to skin cancer, the effectivity and safety of neoadjuvant PDT to surgery has been shown in preclinical trials for the treatment of non-small-cell lung cancer [49], breast cancer (extramammary Paget's disease; EMPD) [50], and mesothelioma [51].

However, research has shown that surgery can induce the production of inflammatory mediators such as IL-6; these inflammatory cytokines can lower the effects of PDT by changing the tumor microenvironment and affecting the immune system [52]. This effect can be extenuated to improve the survival rate by increasing the time interval between surgery and PDT to 6 weeks [53]. Thus, the anti-tumor effect by combining PDT and surgery is worth further exploration in subsequent clinical trials.

PDT Combined with Radiotherapy

PDT combined with radiotherapy (RT) is the second major combination approach in clinical trials (Table 1). PDT-RT has superior therapeutic efficacy over PDT or radiotherapy alone. Decades ago, Calzavara et al. noticed that adjuvant radiation therapy after PDT in esophageal cancer served as an effective treatment for patients [54]. For further confirmation of this observation, an incomplete survey in Japan, from January 1986 to March 1992, showed that PDT and external beam radiation therapy had almost 100% curative power for roentgenologically occult lung cancer (except for noncancerous lethal) [55]. Not accidentally, other clinical data have shown that the combination of PDT and brachytherapy (high dose) was safe and excellent for lung cancer, with no recurrence, no severe complications for 28 patients, and two complications in six patients with metastases (32 patients in total) [56]. Furthermore, PDT followed by ionizing radiation has been reported to be a more safe and well-tolerated palliative treatment to prevent and alleviate suffering, thereby improving the life quality of patients facing life-threatening advanced esophageal cancer [57]. Studies have also demonstrated that ALA-PDT together with deeply penetrated holmium or carbon dioxide lasers had curative effects on patients with extramammary Paget's disease (EMPD), which is a rare and slow-growing intraepithelial neoplasm [58]. Further studies have demonstrated the safety of this combination in EMPD treatment, with fewer side-effects such as refractory ulcers of ionizing radiation [59,60]. Although survival rates after RT can be high in several cancer

types, including early-stage larynx cancer and non-small-cell lung cancer, unfortunately, in some other cancers (glioblastomas and sarcomas), there are tumor recurrences because of hypoxia, surviving cell repopulation during RT, and intrinsic cell radioresistance [61]. When PDT is combined with RT, the RT resistance does not influence the efficacy of PDT. Thus, the treatment sequence can be reversed to start with radiotherapy, followed by PDT [62]. To this point, in a phase I study of PDT as an adjuvant treatment for esophageal cancer, the optimum laser fluence rate of PDT was first determined using talaporfin sodium and a diode laser for patients with local failure after chemoradiotherapy or RT [63]. Thereafter, a multicenter phase II study demonstrated the efficacy of this strategy, with an 88.5% local complete response for local RT failure esophageal cancer patients [64].

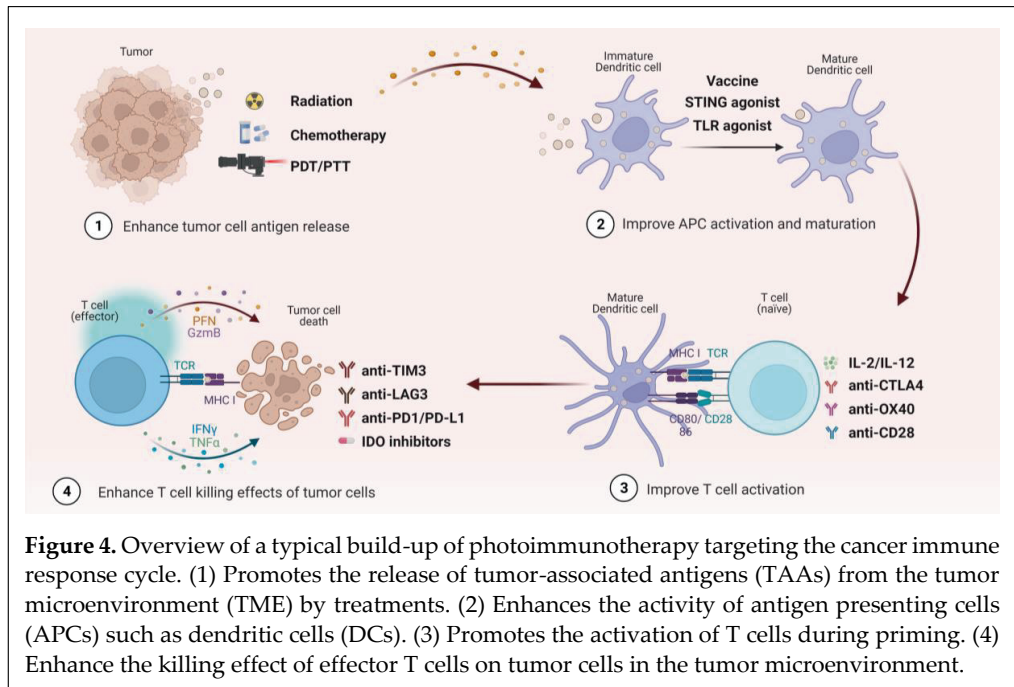
PDT Combined with Chemotherapy

The clinical trials of PDT plus chemotherapy are currently based on first-generation PSs (porfimer sodium, Photofrin®). PDT in combination with standard chemotherapy has been studied in NCT01770132, NCT02082522, NCT00869635, and NCT02662504. Moreover, the possibilities of combination with gemcitabine hydrochloride, S-1, cisplatin, and pemetrexed have been explored. A phase II study (NCT00869635) of PDT combined with systemic S-1 chemotherapy for cholangiocarcinoma showed good tolerance and improved efficacy, with a higher 1-year survival rate (76.2% vs. 32%) and prolonged overall survival (median 10 months vs. 2 months), compared with patients treated with PDT alone [65].

The Potential of PDT in Combination with Immunotherapy by Enhancing Each Steps in Cancer-Immunity Cycle

The basic concept of immunotherapy is to activate the immune system to effectively recognize and remove tumor cells by enhancing the anti-tumor response in the cancer-immune cycle and reducing the evasive effect towards immune defenses (Figure 4) [66]. First, therapies (PDT, radiation, and chemotherapy) can lead to the release of tumor-specific antigens or tumor-associated antigens (TAA). These cancer antigens are then engulfed, processed, and delivered by antigen-presenting cells (APCs), such as dendritic cells (DCs) [67]. Many studies have shown that damage-associated molecular pattern molecules (DAMPs) or pathogen-associated molecular pattern (PAMPs) molecules released from tumor cells after treatments can promote DC activation and maturation [68]. The trend is to use a combination of appropriate therapies to eliminate a sufficient number of cancer cells, thereby providing high levels of DAMPs to initiate an immune cascade to ablate the remaining resistant cells at the tumor site and metastases by abscopal effects [69]. Some immunostimulatory adjuvants, such as CpG oligonucleotides (ODN), cytokines, Toll-like receptors (TLR) agonists, etc., can further amplify its activity by activating a specific pattern recognition receptor (PRR) in the APC, which plays a crucial role in recognizing PAMP and DAMPs. Thus, thereby enhancing the subsequent activation and expansion of naive T cells in the lymph nodes [70]. In addition to promoting a stronger DCs maturation to interact with naive T cells, T cell activation can also be amplified by agonistic monoclonal antibodies against various receptors (e.g., 4-1BB, OX40 (CD134), CD28, CD27, etc.) [71], cytokines (interleukin (IL)-2 and IL-12) [72], and inhibitors of immunosuppressive molecules (anti-cytotoxic T lymphocyte-associated

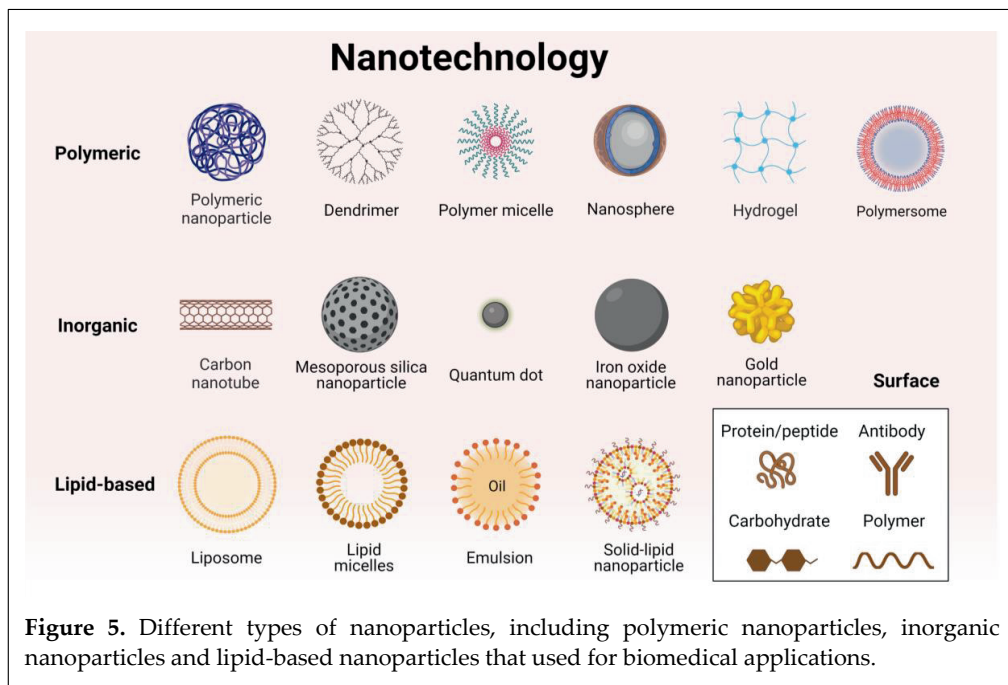
protein 4 (CTLA-4)) [73]. The activated effector T cells then infiltrate into the tumor site to realize its anti-tumor effects. Enhancing the tumor-killing efficiency of effector T cells by blocking immunosuppressive signals in the tumor microenvironment that inhibit T cell activation and function can be a powerful strategy, even for cancers that have metastasized [74]. The most commonly used forms in clinical are immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2 [74,75]. Combining PDT with immunotherapeutic agents is compelling and has shown potential to induce robust antigen-specific immunity and cytotoxic T lymphocytes in cancer treatment.



The Emergence of Nanomedicine as A Delivery Platform in Cancer Therapy

The use of nanomaterials in medical applications is showing exciting results [76]. One of the main nanomedical research is in the direction of tumor-targeted drug delivery to reduce the ineffective distribution of the drug in the organism and to reduce life-threatening side effects, inspired by the concept of the "magic bullet" proposed by Paul Ehrlich [77]. This is because conventional treatments, especially chemo-therapeutic drugs, achieve their anti-cancer effects by blocking abnormal cell proliferation. This non-tumor-targeted killing effect is the main source of adverse side effects on patients and can be effectively addressed by using nanoparticles to deliver drugs to the tumor site [78]. Tumor targeting can be achieved by passive targeting based on the unique scale properties (structures typically between 1-100 nm in diameter) of nanoparticles, enhanced permeability and retention (EPR) effect at the tumor region [79]. However, this effect was confined to larger tumors (<100 mm³), and the EPR effect was limited to undetectable micrometastases. Related to this, active targeting of nanoparticles is an important strategy

through modifications to the nanoparticle surface, and thus nanoparticles can specifically bind to whether metastatic or primary cancer cells (such as specific antibodies, peptides, or receptor ligands) [79]. As delivery carriers, nanoscale properties provide the “stealth” effect and immunocompatibility effect for nanoparticles to protect the encapsulated agents for effective delivery to the tumor site before being degraded and cleared [80]. Thereby, nanoparticles address the inefficiencies of conventional treatments and the dose required for optimal treatment. Until now, researchers have developed different types of nanoparticles for biomedical applications. Figure 5 depicts an overview diagram of nanoparticles commonly used, which can be divided into inorganic nanoparticles composed of metals such as gold and silver or colloids of silicon, and organic nanoparticles composed of lipids, sugars, and (biodegradable) polymers [81]. By modifying the physicochemical properties of the nanoparticles, a continuous, sequential, or slow release of the drug can be achieved under specific stimuli (e.g., temperature, specific enzymes, or pH) [81]. In addition, nanoparticles provide the platform to integrate combined anticancer effects, imaging, or diagnostics by encapsulating, embedding, or attaching multiple drugs simultaneously.



The Scope of This Thesis

In this thesis, we start with a general introduction in **Chapter 1** to briefly present the state of PDT, immune therapies, and nanotechnology in the field of cancer. PDT is a well-established approach in superficial cancer treatment. The aim of my Ph.D. research work has been to improve therapeutic responses in solid tumors by novel combinatorial strategies based on PDT and the utilization of nanotechnology. Insights and concepts in these works are expected to help to design personalized therapeutic interventions in

cancer progression. In **Chapter 2**, we focused on the combination of PDT with a stimulator of interferon genes (STING) agonist: ADU-S100. We investigated the anti-tumor efficiency and survival time after this combined treatment in colon tumor mice models. We found that ADU-S100 post-PDT treatment could enhance PDT-induced inflammation and immune responses, which lead to abscopal effects in a distal untreated tumor. The combination also protected cured mice from tumor recurrence through memory T cell anti-tumor immune responses with high probability. In **Chapter 3**, we found that PDT in combination with viral core particles could prime systematic immune responses and serum antibody intensity to against colon cancer process in MC38 tumor-bearing mice. In **Chapter 4**, we reviewed the current challenges facing the combination of PDT and multiple cancer treatment options based on current published literature. We highlighted the opportunities of nanoparticle-based PDT in cancer therapies. In **Chapter 5**, we investigated how hydrogel-supported near-infrared (NIR) -PDT with improved therapy potential in tumor-bearing mice by combining it with immune checkpoint inhibitors. In addition to the improved tumor growth inhibitory effects and prolonged survival time, immune mechanisms were also studied. We found that hydrogel-supported NIR-PDT by multi-stimulation could induce a higher level of lymphocytes in the circulating blood and increased lymphocytes infiltration into tumor site. A general discussion of overall data observed in this work, and clinical and research prospects related to this thesis are provided in **Chapter 6**.

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