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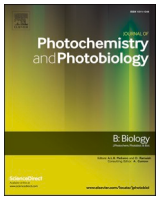

Invited Review

Secure transplantation by tissue purging using photodynamic therapy to eradicate malignant cells

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ABSTRACT

The field of photodynamic therapy (PDT) for treating various malignant neoplasms has been given researchers' attention due to its ability to be a selective and minimally invasive cancer therapy strategy. The possibility of tumor cell infection and hence high recurrence rates in cancer patients tends to restrict autologous transplantation. So, the photodynamic tissue purging process, which consists of selective photoinactivation of the malignant cells in the graft, is defined as a compromising strategy to purify contaminated tissues before transplantation. In this strategy, the direct malignant cells' death results from the reactive oxygen species (ROS) generation through the activation of a photosensitizer (PS) by light exposure in the presence of oxygen. Since new PS generations can effectively penetrate the tissue, PDT could be an ideal *ex vivo* tissue purging protocol that eradicates cancer cells derived from various malignancies. The challenge is that the applied pharmacologic *ex vivo* tissue purging should efficiently induce tumor cells with minor influence on normal tissue cells. This review aims to provide an overview of the current status of the most effective PDT strategies and PS development concerning their potential application in *ex vivo* purging before hematopoietic stem cell or ovarian tissue transplantation.

1. Introduction

Chemo- and radiotherapy have improved survival rates in cancer patients, but these therapies could be detrimental to the ovaries, impairing fertility and endocrine function [1]. One of the options to preserve fertility in these patients is the cryopreservation and transplantation of ovarian tissue [2,3]. However, this strategy cannot be advised for patients suffering from hematological malignancies, such as leukemia and Burkitt's lymphoma. These pathologies have shown a high risk of ovarian contamination, and an autotransplantation of the cryopreserved ovarian tissue could, therefore, potentially lead to a relapse of the primary disease [4–6].

On the other hand, in the case of nonemergency patients for stem cell transplantation, patient-specific (autologous) transplantation can be more advantageous than universal (allogeneic) because of the patient cells expansion challenge. This is due to several reasons, such as immunological compatibility, less chance of cell abnormalities and teratoma formation, less non-relapse mortality, and avoidance of specific technical and ethical challenges of embryo-derived allogeneic cells [7,8]. However, autologous transplantation continues to be limited by the possibility of tumor cell contamination and, thereby, high relapse rates [9,10].

Photodynamic therapy (PDT), as a multidisciplinary field of research with tremendous potential for cancer therapy application, employs

Abbreviations: AlPc, Aluminum phthalocyanine; CMA, chlorin e6-monoethylenediamine monoamide; CAM, chorioallantoic membrane; CML, chronic myeloid leukemia; ZnPcS2P2, di-sulfo-di-phthalimidomethyl phthalocyanine zinc; EPR, enhanced permeability and retention; HAL, hexaminolevulinate; GVHD, graft-versus-host disease; MC540, merocyanine 540; ZnPcH1, mono-α-substituted zinc (II) phthalocyanine; MM, multiple myeloma; NPs, nanoparticles; PheoA, pheophorbide-a; PDT, photodynamic therapy; PS, photosensitizer; PPF, porphyrin-peptide-folate; PET, positron emission tomography; ROS, reactive oxygen species; $^1O_2$, singlet oxygen; YAP/TAZ, yes-associated protein/transcriptional co-activator with PDZ-binding motif; ZnPc, zinc phthalocyanine; TH9402., 4,5-dibromorhodamine methyl ester.

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photochemistry and photophysics sciences to eradicate malignant cells. PDT has been used in numerous studies since its first inception in the early 1900s [11]. Presumably, Jesionek et al. were the first to try to employ this method to treat malignancies [12]. In 1972, Diamond et al. [13] showed that hematoporphyrin could be used to treat cancers in animals successfully. Two years after, Thomson et al. [14] reported using acridine orange that had been exposed to an argon laser to treat a mouse epithelial tumor, and finally, the first formal presentation by Dougherty et al., in 1975 [11]. They found fluorescein diacetate's ability to damage TA-3 cells in vitro photodynamically and then started administering fluorescein to animals with tumors, discovering that it may act as a photosensitizer [15,16]. Progressively, it has evolved as a unique therapeutic modality at the disease site. In comparison with radio- or chemotherapy and surgery, which is mostly immunosuppressive, PDT possesses several considerable advantages due to its relatively non-invasive property, selectivity, reduced long-term morbidity, and the ability of precise targeting [17,18]. The PDT's main component is a photosensitizing chemical substance called photosensitizer (PS). It can produce reactive oxygen species (ROS) once activated light exposure in the presence of oxygen [19–21]. Besides neoplastic conditions, PDT is a promising methodology to treat other disorders, such as atherosclerosis [22–24], psoriasis [25–27], age-related macular degeneration (AMD) [28–30], inactivation of microorganisms [31–33] and autoimmune diseases [34–36]. The exposed light type can affect the PS phototoxicity via various wavelengths, energy density, and exposure time [37,38].

Among some perspectives, such as addressing immunological issues and finding an acceptable solution to induce pluripotent stem cells to meet clinical safety requirements, one of the most exciting ideas is to address the cell purity issue by PDT purging [8]. For example, the *ex vivo* PDT purging strategy benefits cancer patients with a high risk of ovarian tissue metastasis, which must preserve their fertility after their disease treatment.

This review aims to provide an overview of the most significant PS developments and recent studies on the application of *ex vivo* PDT purging before hematopoietic stem cell and ovarian tissue transplantation.

2. PDT therapeutic mechanism

The cytotoxic ROS and $^1O_2$ can be generated, followed by the transition of irradiated PS from the low-energy ground state to a short-lived singlet-excited state (^{1}PS*). This transition may cause two pathways: (i) emitting fluorescence by falling back to the ground state, which has the potential to be used for clinical photodetection and imaging; or (ii) spinning its excited electron inverts to form a triplet-excited PS (^{3}PS*) by an intersystem crossing (Fig. 1). The ^{3}PS*generation with lower energy level and relatively longer life can cause transferring of absorbed energy from their triplet-excited states to surrounded oxygen molecules, creating either cytotoxic ROS, such as hydrogen peroxides, superoxide anion and hydroxyl radicals (type I reaction) or singlet oxygen ($^1O_2$), which is a singlet-excited state of oxygen (type II reaction) [39,40]. Types I and II can co-occur, and their possibility ratio depends on the used PS. Still, since type II plays a vital role in the therapeutic effect of PDT, it is the only indicated type in the studies [41]. The PDT efficiency of different PSs depends mainly on their $^1O_2$ quantum yield as highly effective physicochemical parameters, which means the amount of singlet oxygen generation per photon absorbed by the PS [42,43]. Finally, the generated species can react with biomolecules and leads to cancer cell death through three pathways: (i) necrosis, apoptosis, and autophagy, (ii) vascular injury and tumor ischemia; and (iii) activation of the host immune system against tumor antigens [44–47].

3. PDT Disadvantages

Despite the many advantages of PDT, several issues have limited its development. Due to the poor penetration of UV/visible light into biologic tissues, PDT mostly has a superficial impact and can be used to treat tumors just under or on the outer lining of internal organs and cavities, such as premalignant conditions, in situ carcinoma, and superficial malignancies [48–51]. To address the poor penetration depth of typical PDT, several researchers are attempting to employ alternative excitation sources besides light, such as chemiluminescence-based systems [52,53], Cerenkov [54,55] and x-ray radiation [56,57]. Another drawback of the majority of common PSs is their tendency to self-aggregation in an aqueous biologic medium due to their low solubility, resulting in poor bioavailability and off-target activation [41,46,58–60]. This may also affect their photosensitivity and photophysical properties due to their poor pharmacokinetics [41,46,58–60]. In the third-generation PSs, the low solubility issue is addressed by chemical/structural modification or the use of nanocarriers encapsulation/conjugation.

4. Photosensitizers

PSs are usually innocuous dyes when the radiation is not applied [61]. According to their development, they have been categorized as first-, second-, and third-generation (Fig. 2) [41,62]. The first-generation PSs, which mainly were hematoporphyrin derivatives or porfimer sodium (Photofrin®), including porphyrin monomers, dimers, and oligomers, were developed in the 1970s and early 1980s [19,63]. Since PS' properties are highly dependent on their physicochemical features, such as hydrophobicity, charge-to-mass ratio, and the number of chemical rings, the PS development was mainly based on chemical modification of their structure. For instance, chlorine has been introduced as a reduced form of porphyrin by reducing one peripheral cross-conjugated bond. Therefore, second and third-generation PSs have been developed to improve some disadvantages of first-generation PSs, such as low phototoxicity specificity, poor light absorption in the spectrum portion with optimal light penetration in tissue, and low uptake efficiency [41,45,64–66].

In the late 1980s, the second-generation PSs were introduced and had higher chemical purity and yield of $^1O_2$ formation. Another

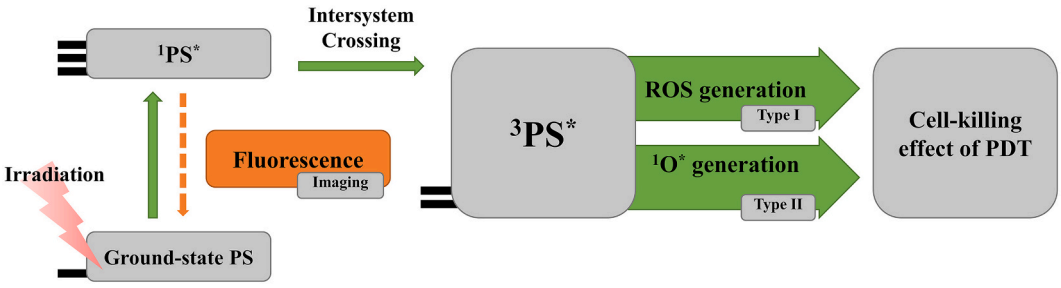

Fig. 1. Diagrammatic explanation of PDT therapeutic effect; irradiated PS transition from the ground-state to ^{1}PS* will take one of two routes: emitting fluorescence by dropping back or rotating the excited electron inverts to form a ^{3}PS* by an intersystem crossing, which causes generating ROS or ^{1}O* from surrounded oxygen molecules [47].

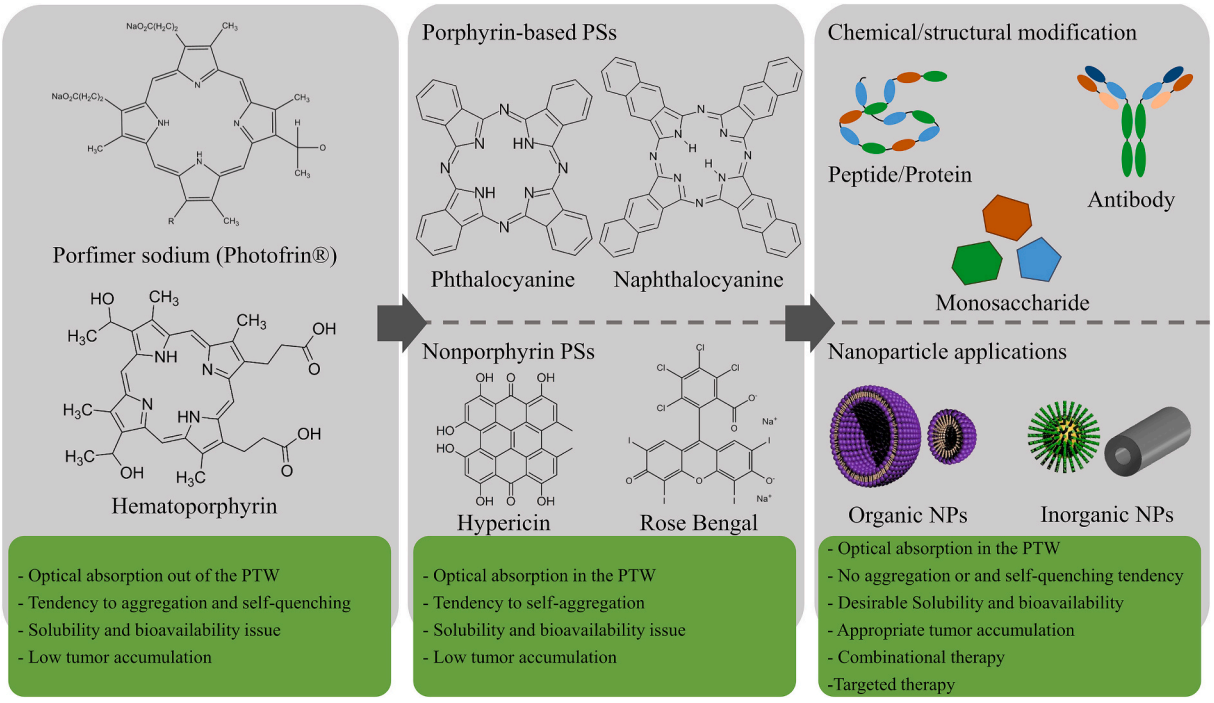

Fig. 2. Schematic overview of the chronological evolution of first-, second-, and third-generation PSs. PTW: phototherapeutic window (600–850 nm) [41,62].

advantage of second-generation PSs is that they are activated in wavelengths between 650 and 800 nm. Since this wavelength range includes the biological tissue's optical window, the exposed light can be strongly absorbed by the PS and poorly by the tissues [39,40]. Additionally, the lights with wavelengths between 600 and 1000 nm possess deeper penetration and lower absorption in biological tissue compared to the wavelengths between 400 and 600 nm (Fig. 3) [67–69]. Since the absorption spectrum of hematoporphyrin derivative has a peak of approximately 400 nm, the proper light for its activation has poor penetration. Hence, it cannot be used for purging tumors with more than 2 mm thickness. However, activating wavelengths for second- and third-generation PSs are more penetrating (5–10 mm) [70]. Besides, third-generation PSs have been developed to maximize tumor selectivity, improve PDT efficiency by optimizing optical/photochemical properties and eradicate some unfavorable PSs pharmacokinetics [71,72].

Up to now, there were two main ways to introduce third-generation PSs: applying chemical/structural modification on second-generation PSs or using PSs encapsulated/conjugated nanoparticles (NPs) such as PLGA (Poly(D,L-lactide-co-glycolide))-NPs [73–75], PCL (poly(ε-caprolactone))-NPs [76–78], PGA (Poly (γ-glutamic acid))-NPs [79,80], TiO_2 (Titanium dioxide)-NPs [81–83], gold-NPs [84–86], silica-NPs [87–89], micelles [90–92] and liposomes [93–98], to dedicate some special properties, such as controlled release profile, deeper penetration, targeting, aqueous solubility, and MRI-guiding, on PSs. Moreover, due to the increased permeability and retention (EPR) effect and increased surface-area-to-volume ratio (SA/V), these nanosystems could help PDT agents be more tumor-selective and have better cellular uptake [99–107].

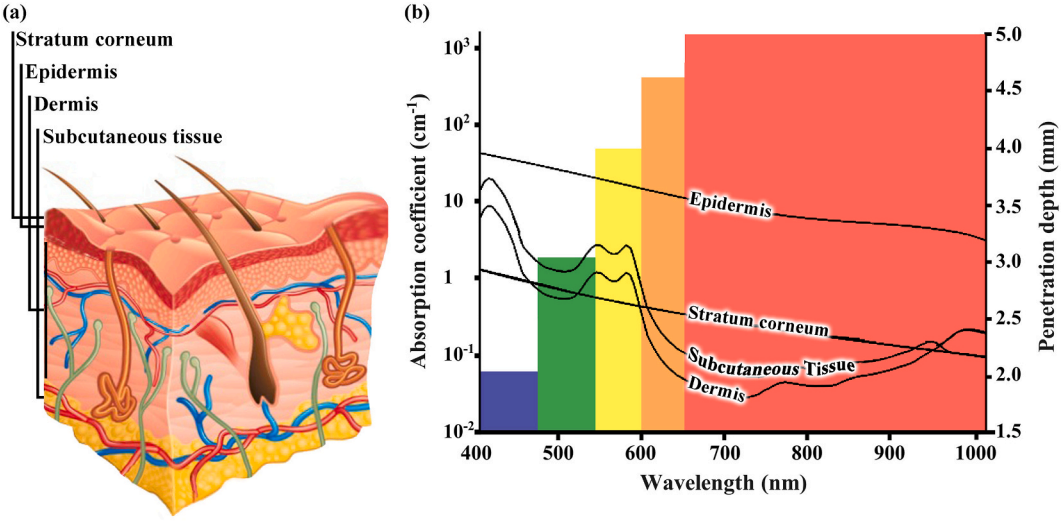

Fig. 3. Anatomical schematic of different skin layers, including stratum corneum, epidermis, dermis, and subcutaneous adipose tissue (a) (Reprinted and adapted from Agarwal S, Krishnamurthy [108] with permission from the Creative Commons (www.creativecommons.org)), the absorption spectra [109], and the penetration depth of light with different wavelengths in the mentioned layers of human skin tissue [110] (b).

5. *In Situ* PDT Purging Application

Topical PDT for tissue purging is mainly applied for skin lesions using a combination of PS creams and light exposure steps. There are mainly two categories of malignant skin tumors: melanoma and non-melanoma malignancy. One of the most challenging issues regarding skin transplantation is the prevalence of actinic keratosis and non-melanoma skin cancer in organ transplant recipients. Unfortunately, due to the long-term immunosuppressive therapy, the prevalence of the malignancy is considerably high in these recipients compared with immunocompetent patients [111]. Topical PDT has recently become a good option for treating actinic keratosis and basal cell carcinoma [112]. Wennberg et al. studied topical PDT efficiency using methyl aminolevulinate cream (160 mg/g) and illumination with noncoherent red light (630 nm, 37 J/cm^2) to prevent new skin lesions in transplanted recipients and reported a 46% occurrence reduction of actinic keratosis [113]. In another study, Wulf et al. reported 62% eradication of new lesions 12 months after treatment with the same protocol for renal transplant recipients [114]. Moreover, due to its higher complete resolution rate and more significant lesion area reduction, MAL-mediated PDT showed to be more effective for the post-transplant epidermal dysplasia treatment than topical 5% fluorouracil (5-FU) cream[115]. Despite these positive results, *in situ* PDT-based purging is not possible for tumors located in deeper body sites (>10 mm). For such cases, when possible, one can propose the removal of the affected tissue/organ and its decontamination through *ex vivo* PDT application.

6. *Ex Vivo* PDT Purging Applications

The ideal *ex vivo* tissue purging protocol would involve the pharmacologic eradication of cancer cells derived from various malignancies. The inhibitory molecules should be small enough to allow for efficient penetration into the tissue. One of the most common pathways for *ex vivo* tissue purging is using different inhibitors, such as nicotinamide (SIRT1 inhibitor) [116,117] and GSK1070916 (Aurora B/C kinase inhibitor) [118]. One of the effective physiological targets for the *ex vivo* treatment is the Hippo pathway (also defined as the Salvador-Warts-Hippo Pathway), an emerging pathway for growth control and tumor silencer that regulates cell proliferation, apoptosis, and stem cell function. Yes-associated protein/transcriptional co-activator with PDZ-binding motif (YAP/TAZ) are two Hippo signaling downstream effectors and contribute to cancer tumor development [119–121]. Although the Hippo pathway has been shown to have dysregulation in different types of cancer, YAP/TAZ pharmacological inhibitors can be an effective strategy to purge a tissue fragment from cancer cells types such as breast cancer [122–124], rhabdomyosarcoma [125–127], liver cancer [128–130] and leukemia [131–133].

The selectivity and efficacy of PDT methodology depend on multiple conditions, such as the PS type and generation, wavelength and energy density of exposed light, the PS/cells incubation time, and the environment oxygen concentration [65,134]. The *ex vivo* PDT purging strategy has been employed for bone marrow grafts [135,136]. Recently, it has also been considered for cancer cell purging in ovarian tissue before transplantation [137,138].

6.1. Fertility Preservation by Ovarian Cryopreservation and Transplantation

Nowadays, ovarian tissue cryopreservation and transplantation is the only alternative for prepubertal girls and women undergoing immediate treatment for cancer to preserve their fertility. The immature follicles in the frozen-thawed ovary fragment will restart their growth in the remaining ovary after transplantation [1,2]. However, there is a serious question for patients suffering from some forms of cancer, which has a high risk of ovarian tissue contamination. Nevertheless, there is an incredibly fascinating and daunting strategy that purges ovarian tissue from malignant cells before autotransplantation, among other alternatives to avoid malignancy, such as *in vitro* follicle development and artificial ovary [4,5,139–144] (Table 1). One of the most crucial conditions for ovarian cortex tissue is that the purging procedure should not impair follicular function or damage the ovarian stromal cells [137]. In this respect, the PDT eradication process can be implemented due to its selective phototoxicity for malignant cells. Fig. 4 reveals the PDT purging process strategy architecture before ovarian tissue cryopreservation and transplantation.

Previously, the sensitivity of the ovarian carcinoma cells to PDT has been determined in some studies [145–147]. In 1999, a derivative of chlorine, mesotetra(hydroxyphenyl)chlorin (m-THPC), was employed with irradiation by diode laser (652 nm) to eliminate ovarian cancer cells from a mouse xenograft model, which showed over seven times more necrosis than control tumors [145,146]. In the same year, Ismail et al. [147] evaluated the influence of PDT on human ovarian fresh biopsies contaminated with malignant tumors cultivated on the chorioallantoic membrane (CAM) using free methylene blue (MB) and MB-loaded liposomes. The PDT was done 4–5 days after implantation, using 1-h incubation with 0.1 mM of the PSs before the krypton laser irradiation (647 nm, 100 J/cm^2), and five days after PDT, tissue remission was observed in all the treated tumors [147]. The phototoxicity of chlorin e_6-monoethylenediamine monoamide (CMA), as a derivative of chlorin e_6, was also tested against ascites or pleural fluid cells from 15 patients with ovarian and non-ovarian cancers. The purging by 3 μM CMA followed by an argon ion-pumped dye laser irradiation (654 nm, 25 J/cm^2) demonstrated a statistically significant difference between the viability of these two groups and considerable specificity and sensitivity of antigen-binding, which is efficient enough for cell targeting and selective photochemical elimination, and thereby a promising potential for further assessment as photochemotherapeutic agents [148].

Recently, Mulder et al. [137] made an *ex vivo* tumor model via microinjection of cancer cell lines (embryonal rhabdomyosarcoma [RD and Rh36], alveolar rhabdomyosarcoma [Rh5], Ewing's sarcoma [ES-2], BC [MCF7], and chronic myeloid leukemia (CML) [K562]) in ovarian cortex fragments (5 × 10 mm) and studied on their purging efficiency followed by 24h incubation with 3.0 μM Verteporfin. The results showed that it is possible to effectively purge ovarian cortex tissue from malignant cells by short-term *ex vivo* treatment using specific YAP/TAZ inhibitors. In addition, their *ex vivo* tissue purging method may not impair the function of ovarian cortex tissue due to the lack of detrimental effects of a 24h Verteporfin treatment on the small follicles (primary and primordial) morphology and of small follicles' viability directly after treatment [137].

Currently, our team is studying the PDT purging efficiency of leukemia cells microinjected ovarian tissue fragments using various PDT protocols; (i) OR141 and OR141-loaded niosomal nanoparticles, both with daylight LED irradiation; and (ii) aluminum (AlPc)/zinc-based tetracarboxylic phthalocyanines (ZnPc), using the irradiation by 660 nm diode laser with various energy densities. Our results showed that niosomal formulation could increase PS selectivity and penetrability for *ex vivo* PDT-purging malignant cells from ovarian fragments. In addition, two other PDT processes, including AlPc-based PDT (irradiated energy density: 10 J/cm^2) and ZnPc-based PDT (irradiated energy density: 50 J/cm^2), both in the range of 0.5–1 μM, showed high potential for this regard due to the ability of eradication of malignant cells without any significant phototoxicity for isolated ovarian stromal cells. The results are very promising, and further investigation will include the study of the treatment effect on *in vivo* test by xenografting PDT-treated ovarian fragments in nude mice to test the impact of the PDT protocol on follicle survival and development [138].

6.2. Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation, the transplantation of bone

Table 1
Ex vivo strategies to eradicate malignant cells from ovarian tissue.

Malignancy	Purging goal	PS	Conclusion	Ref.
Leukemia	Purging ovarian cortex fragments contaminated by leukemic cells by PS-loaded NPs	OR141, niosomal OR141	Niosomal OR141 could eradicate the tumors in *ex vivo* models with a considerable declination in cancer cell proliferating rate	[149]
Leukemia	PDT efficiency of aluminum/zinc-based tetracarboxylic phthalocyanines on ovarian stromal cells vs. cancer cells	AlPc, ZnPc	AlPc and ZnPc irradiated by a 660 nm diode laser with energy densities of 10 and 50 J/cm^2, respectively, showed the most selective eradication of malignant cells without any significant cytotoxicity for ovarian stromal cells	[138]
Rhabdomyosarcoma, leukemia, breast cancer	Eliminating metastasized cancer cells without compromising the ovarian tissue or follicles	Verteporfin	The small tumors derived from leukemia and rhabdomyosarcoma were efficiently eradicated from human ovarian tissue fragments by *ex vivo* pharmacological specific inhibition of YAP/TAZ	[137]
Ovarian cancer	Evaluation of the photo-immunotherapy efficacy in ovarian cancer cells	CMA	High cytotoxicity was exhibited in ovarian cancer cells with minimum damage on non-ovarian cancer cells, which shows the selectivity of the method	[148]
Ovarian cancer	Malignant cells eradiation from ovarian tumor grafted CAM	Free and liposomal methylene blue	Both approaches indicated an effective PDT for treating the ovarian malignancies	[147]

Abbreviations: aluminum phthalocyanine, AlPc; chlorin e_6-monoethylenediamine monoamide, CMA; chorioallantoic membrane, CAM; Nanoparticles, NPs; yes-associated protein/transcriptional co-activator with PDZ-binding motif, YAP/TAZ; zinc phthalocyanine, ZnPc.

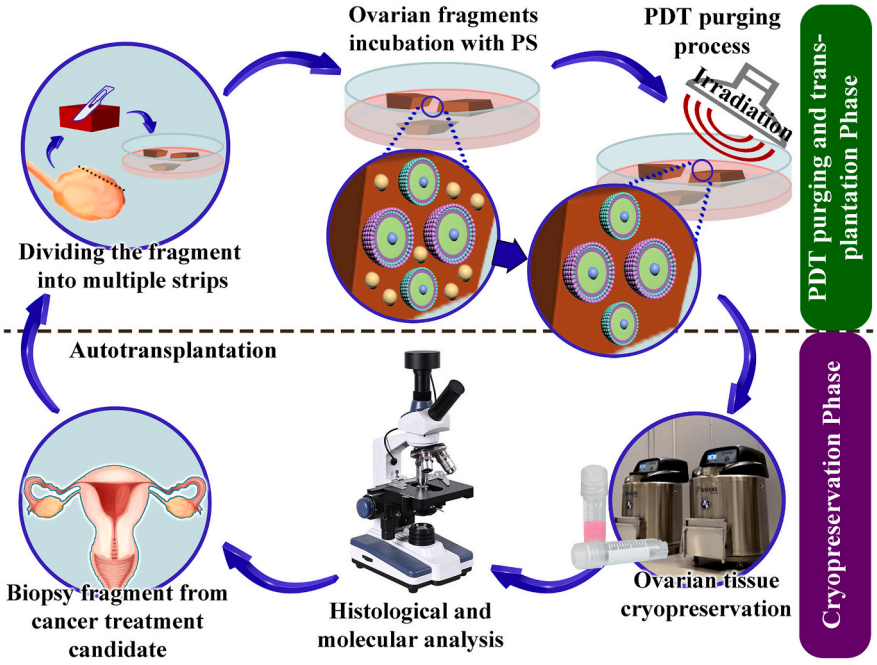

Fig. 4. Schematic plan for utilizing PDT purging process before ovarian transplantation.

marrow-derived and peripheral blood-derived hematopoietic stem cells, which can be autologous (Auto-HSCT) or allogeneic (Allo-HSCT), offers a possible cure for hematologic malignancies such as leukemia, multiple myeloma (MM), and lymphoma, as well as several solid tumors like breast and ovarian cancer [150,151]. Over the last decades, various intensities of high-dose regimens have been developed explicitly for these patients, and nowadays, there are three main techniques commonly used: (i) myeloablative (MA), (ii) reduced-intensity conditioning (RIC), and (iii) non-myeloablative (NMA) regimens [152,153]. Due to the impairment of hematopoietic stem cells after the treatment, HSCT is essential to rebuilding blood and the immune system [154,155].

6.2.1. *Malignant Cells PDT Purging for Auto-HSCT*

Auto-HSCT possesses several advantages over Allo-HSCT, such as more rapid hematopoietic reconstitution, easier graft transplantation, slight age limitation, lower risk of life-threatening complications, and treatment-related mortality [156,157]. However, Auto-HSCT still has its restriction of high relapse rate due to the risk of cancer cells contamination and therefore, as well as ovarian cancer, selective eradication of malignant cells is essential for grafts in auto-HSCT. Various methods have been used to purge the bone marrow of remaining malignant cells, including immunotoxins and pharmacological purging (Table 2). These efforts, however, have been hampered by the non-specific cytotoxicity of chemotherapy drugs like 4-hydroxyperoxycyclophosphamide and the absence of monoclonal antibodies to well-recognized leukemia antigens [158]. Fig. 5 illustrates the strategy design of the PDT purging mechanism before Auto-HSCT. Bone marrow *ex vivo* purging by Merocyanine 540 (MC540)-mediated PDT has been used for phase I/II clinical *ex vivo* purging Auto-HSCT grafts from leukemia and lymphoma malignancies [159,160].

Anderson et al. investigated the safety and efficiency of a combination of MC540-PDT and Edelfosine for the *ex vivo* purging of autologous stem cell grafts from BC patients. In this study, the tumor cells (human and murine BC cell lines) and normal bone marrow cells were treated with MC540 with the concentration of 15 μg/ml and 60 min light exposure (tubular white fluorescent light bulbs, 27 W/m^2), then the

Table 2
Ex vivo purging to eradicate various malignancies cells before HSCT.

Malignancy	Purging goal	PS	Conclusion	Ref.
MM, BC	Obtaining optimized PDT protocol to improve the selectivity of drug retention between neoplastic cells and normal stem cells	TH9402	The *ex vivo* PDT test on stem cell samples demonstrated the safety of TH9402-mediated PDT for normal hematopoietic stem cells while inducing more than 5 logs of MM and BC cell lines eradication	[162]
CML, Non-Hodgkin leukemia, metastatic breast cancer	Safe eradication of neoplastic cells to reduce the relapse rate after transplantation	TH9402	*Ex vivo* PDT purging by TH9402 was recognized as a safe treatment of malignant cells via the lack of damage to normal human hematopoietic stem cells	[163]
Breast cancer	Reducing the relapse risk after Auto-HSCT	MC540	Cancer cells were eradicated selectively and effectively using a combination of MC540 PDT and Edelfosine	[135]
Lung cancer	Determining the CV-PDT efficiency for preclinical purging from solid tumor and drug-resistant mutant tumor cells	MC540, CV	Using CV in combination with MC540 showed clinically meaningful tumor cell depletion	[161]
Erythroblastic leukemic	Effective PDT purging of bone marrow to have safer transplantation in mice	ZnPcS2P2	Promising results in the eradication of malignant cells and purging bone marrow auto-grafts associated with the hematopoietic activity via the persistence of enough progenitor cells	[165]
CML	Evaluating a novel modality for auto-HSCT grafts purging from CML cells	ZnPcH1	CML cells were more sensitive to ZnPcH1-PDT than healthy progenitors of granulocytes/ macrophages	[166]
Breast cancer	Eradication of 4T1 malignant cells from *ex vivo* model to have a safer transplantation	HAL	HAL-based PDT purging may be a beneficial technique for treating animals with experimental BC	[164]

Abbreviations: 4,5-dibromorhodamine methyl ester, TH9402; chronic myeloid leukemia, CML; di-sulfo-di-phthalimidomethyl phthalocyanine zinc, ZnPcS2P2; hexaminolevulinate, HAL; Merocyanine 540, MC540; mono-α-substituted zinc (II) phthalocyanine, ZnPcH1. Multiple myeloma, MM;

treatment was fulfilled by 1-h incubation with Edelfosine. The BC cells were significantly degraded, while the normal hematopoietic stem and progenitor cells were only minimally damaged [135,136]. In another study, a combination of MC540 and crystal violet, as a small cationic amphipathic PS, was successfully employed for a preclinical purging model from H69 human small lung cancer cells and cisplatin-resistant mutant H69/CDDP cells [161].

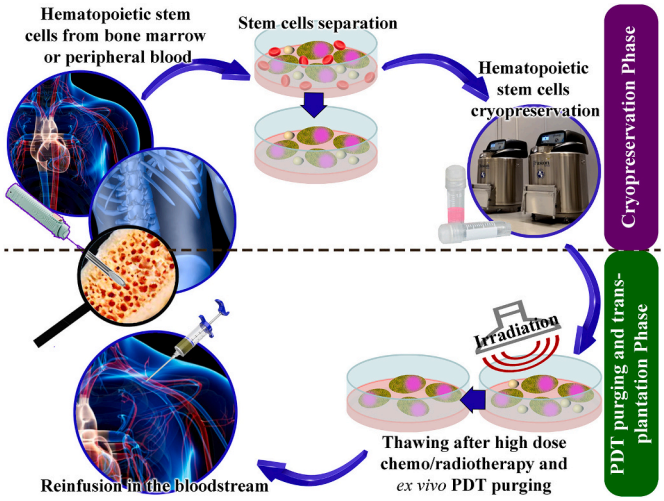

Fig. 5. Idea plan schematic for utilizing PDT purging process before Auto-HSCT.

Brasseur et al. [162] evaluated the potential of the PS, 4,5-dibromorhodamine methyl ester (TH9402), which is a derivative of dibrominated rhodamine to optimize the eradication of MM and BC cell lines. The independent variables, including cell concentration, suspension thickness, PS dose, and light, were chosen to have the lowest inconveniency for normal pluripotential blood stem cells. As a result, complete malignant cell lines eradication associated with an acceptable hematopoietic progenitor cells recovery and promising outputs for auto-HSCT *ex vivo* purging was obtained by 40 min incubation of the cell suspension (thickness:2 cm, containing 20×10^6 cells/mL) with 5–10 μM of TH9402 followed by 5–10 J/cm^2 (2.8 mW/cm^2) irradiation [162]. This kind of PS was previously used for *ex vivo* purging bone marrow from chronic myelogenous and non-Hodgkin leukemia with a high survival rate of normal human hematopoietic stem cells [163].

In 2011, another study on PDT purging of *ex vivo* models of bone marrow grafts contaminated by metastasized 4T1 BC cells using hexaminolevulinate (HAL), a hexyl-ester of 5-aminolevulinic acid (ALA) followed by their transplantation into 6–8 week-old mice. The animal survival findings and the percentage of 4T1 metastases indicate that HAL-based PDT purging helps BM eliminate the 4T1 tumor cells and saves adequate quantities of BM progenitor cells from guaranteeing hematopoietic reconstruction [164]. Moreover, the purging effect evaluation of di-sulfo-di-phthalimidomethyl phthalocyanine zinc (ZnPcS2P2)-based PDT, as an amphipathic photosensitizer, was studied on murine erythroblastic leukemic EL9611 cells. In this study, the cell mixture of murine erythroblastic leukemic EL9611 and bone marrow cells from normal BALB/c mice, as an *ex vivo* model, was incubated with 4 μg/ml ZnPcS2P2 for 5 h and after the irradiation step by a semiconductor laser (670 nm, 2.1 J/cm^2), transplanted to mice. Fewer leukemia cells in the mixture, longer survival time in mice transplanted with the purged bone marrow, and the maintenance of appropriate progenitor cells for hematopoietic function showed successful Auto-HSCT purging [165]. There is also another report about *ex vivo* PDT purging of bone marrow mononuclear cells suspension contaminated with CML cells (K562) by utilizing 0.5 μM of mono-α-substituted zinc (II) phthalocyanine (ZnPcH1) and photo-irradiated (670 nm, 1.9 J/cm^2). The results show a selective elimination of CML cells with low damage to normal granulocyte/macrophage progenitors [166]. Besides malignant cells, PDT has been used for purging bacterial and viral pathogens from the blood and hematological auto-grafts [167,168].

6.2.2. PDT for T-Cell Depletion in Allo-HSCT

Although allo-HSCT has been recognized for various hematopoietic malignancy diseases as a curative therapy, graft-versus-host disease (GVHD) remains a significant cause of morbidity and mortality, and PDT has been shown to be a preventive therapy that can act by causing tolerance for GVDH and tissue rejection [169,170]. The effects of MC540-PDT on *in vitro* mechanisms of murine lymphocytes and a successful GVHD prevention in murine models of allogeneic bone marrow transplantation were documented by Trail et al. [171]. In another study, Chen et al. [172] investigated the possibility of selective depletion of donor mice alloantigen-specific T cells after *in vivo* grafting of TH9402-PDT purged bone marrow cells to prevent GVDH associated with the maintenance of graft-versus-leukemia effect. The results demonstrated that 90% of recipients survived more than 100 days without detectable tumor cells or causing GVHD while the immunological anti-leukemia functions preserved, which is important to have a protective immunity in clinical allogeneic bone marrow transplantation [172].

7. PS Quantification in Tissue Experiments

Monitoring the PS content, $^1O_2$-tissue interaction, and O_2 saturation level in an *ex vivo* model may improve clinical PDT purging protocols. To calculate the content of PSs in an *ex vivo* model, there are generally two categories of calculation methods; extraction methods in which the PS should be isolated from the tissue and non-extraction methods in which the PS concentration can be estimated in intact tissue [173]. Schlothauer et al. [174] studied the *ex vivo* application of two photosensitizer formulations, pheophorbide-a (PheoA) and perfluoroalkylated zinc phthalocyanine (F64PcZn), in pig ear skin fragments, a good model for human skin. Interestingly, the fluorescence monitoring of PheoA and F64PcZn in pig ear skin biopsies was taken by using a non-extraction method, unveiling the fact that the amphiphilic PheoA could penetrate only the stratum corneum. At the same time, the highly hydrophobic F64PcZn could be found in deeper layers of the epidermis, below the stratum corneum (Fig. 6a,b) [174]. Compared with the fluorescence-based extraction method, non-extraction quantification can usually be done non-invasive and real-time so that they can be applied not only for *ex vivo* tests but also for *in situ* and *in vivo* studies. In 2001, a laser-induced fluorescence (LIF) (Fig. 6c) method was designed as a reliable technique to measure the PS (Aluminum phthalocyanine disulfonate sodium; $AlPcS_2$) concentration in skeletal muscle and liver tissues by fluorescent-based quantifying *in vivo* and *ex vivo*. The LIF quantification demonstrated a 15% variance in liver and muscle response, which may indicate spatial calibration changes due to the delivery of compartmental PS between vessels and stromal tissues [175].

In the case of using PSs without autofluorescent ability, radiolabeling is an alternative for nonintrusive PS quantitation. The PS can be bonded to γ- or positron-emitting radionuclides and detected by nuclear medical imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography [176,177]. Pandey et al. [178] studied a porphyrin-based PS, which is labeled with ^{124}I-derivative, as a radionuclide having a long half-life (~100h) to test the tumor uptake efficiency *in vitro* by using PET imaging of two different models (RIF and Colon-26) in different time points (Fig. 7a) [178]. In another study, incorporating ^{64}Cu into a porphyrin-peptide-folate (PPF) was employed to have a desirable biodistribution, favorable pharmacokinetics, and selective tumor uptake (Fig. 7b) [179]. There are also several reports of using other types of radionuclides for PSs' labeling, such as ^{68}Ga [180–182], ^{109}Pd [183,184], ^{125}I [185], and ^{57}Co [186,187].

8. Nanoparticles Application for PDT Purging

Over the past decades, the combination of PDT and nanomedicine have been attracted the researchers' attention because of their ability to behave as multifunctional nanosystems and to participate in the activation process of PS excitation by either functioning as PSs themselves (e.g., fullerenes and titanium or zinc dioxide NPs) [188–190] or as energy transducers (e.g., gold NPs and quantum dots) [191–193]. Moreover, one of the most important benefits of using NPs in the PDT purging process is that the PS-loaded NPs can increase the purging efficiency by (i) increasing the chance of diffusion and remaining in tumor sites because of the EPR effect [194,195], (ii) increasing the PSs uptake in tumor site due to having a sizeable SA/V [99–101], and (iii) improving the PS bioavailability in the biological environment by helping to overcome PS solubility issues [62,196,197]. Besides, passive targeting caused by specific NPs' characteristics (e.g., size, morphology, and surface charge) as well as active targeting using surface-modified targeted NPs, which can increase the biodistribution and prevent non-specific accumulation, can be employed to decrease the PSs' side effects on normal tissue [198–206]. Moreover, numerous exciting studies on the PDT/nanomedicine multifunctional approaches such as chemo/photodynamic therapy and optical imaging/PDT [207–211].

Numerous types of NPs, such as nanovesicles, nanospheres, nanocapsules, carbonic NPs, and gold NPs, are used to load diverse PSs. The loaded PS is typically released by a mixture of degradation and diffusion processes, and the profile of their release depends on (i) the loading type of the PS, which can be encapsulated, surface-bonded, and matrix-adsorbed; (ii) its diffusion through the matrix and the wall of the carrier; and (iii) the degradation rate of NPs [212–214]. Therefore, in comparison with free PSs, PS-loaded NPs have different kinds of existence in the medium, a time-depended increasing portion of PSs is released and acts like free PSs, and the rest is grabbed by NPs, but

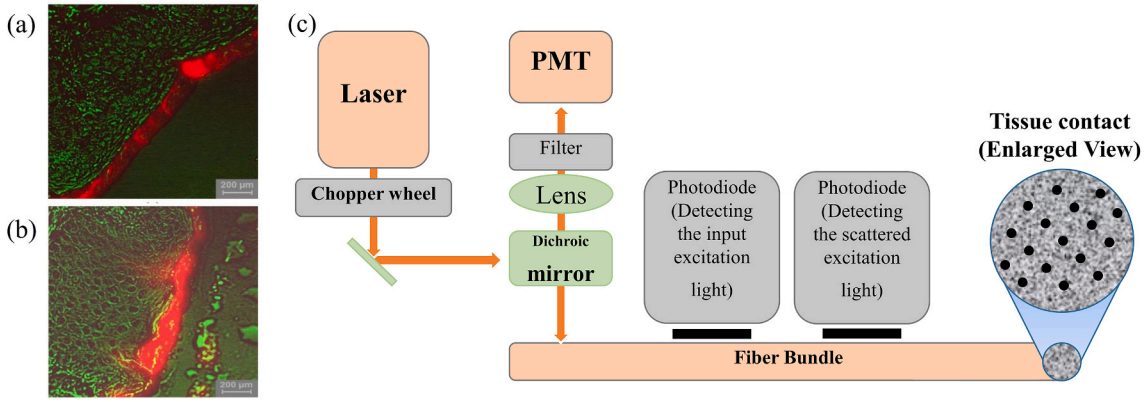

Fig. 6. Fluorescence microscopy imaging to monitor the PSs on pig ear skin biopsies (a) PheoA, (b) F64PcZn (Reprinted with permission from Schlothauer et al. [174] Copyright (2012) Spie), and (c) schematic representation of the fiber-optic bundle system using LIF evaluation (redrawn from ref. [175]). Abbreviation: photomultiplier Tube sensitivity, PMT.

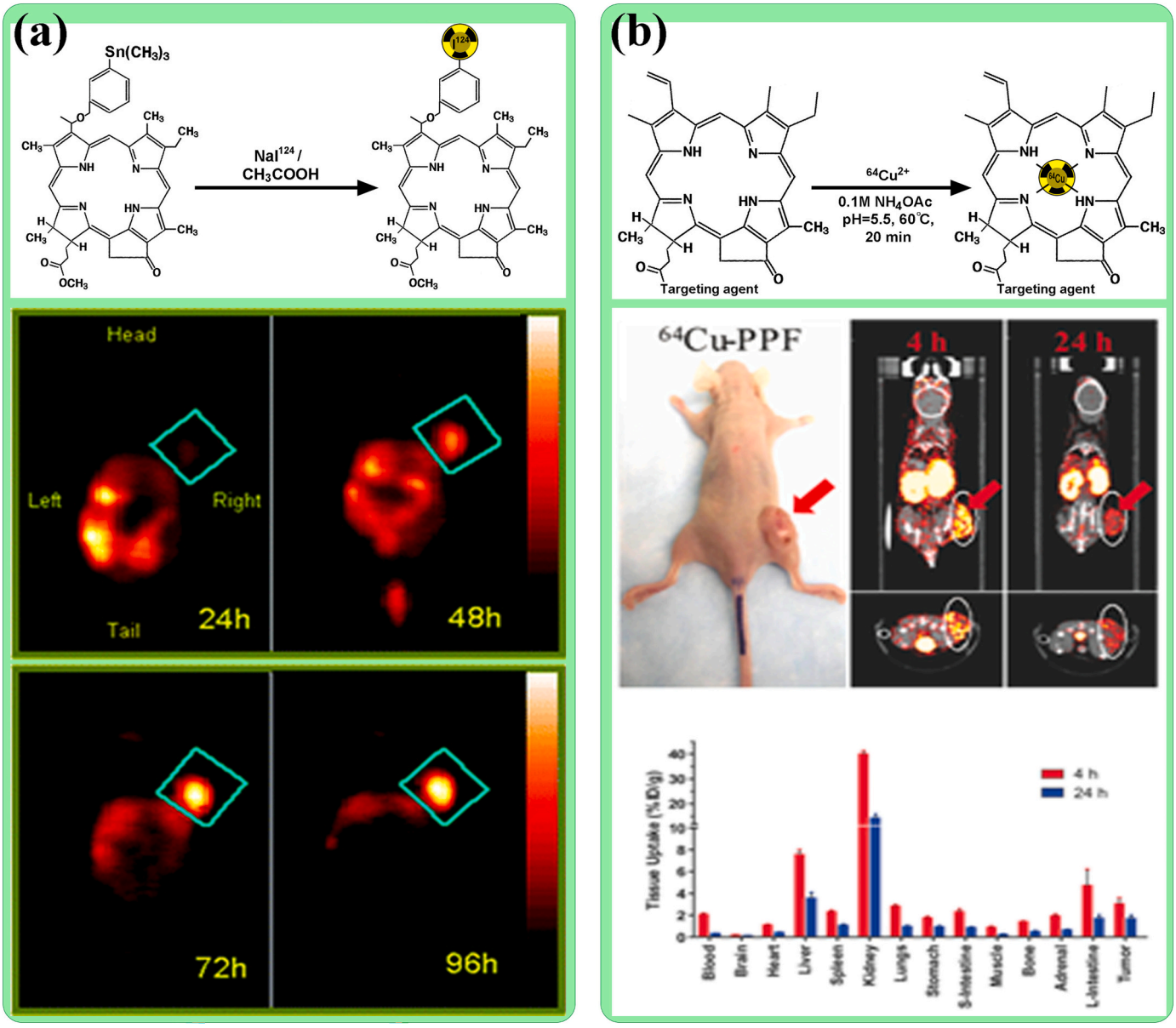

Fig. 7. PS quantitation using radiolabeling: (a) synthetic reaction of porphyrin-based PS labeling by a ^{124}I-derivative and the PET images of a BALB/c mouse bearing Colon-26 tumors on the right shoulder injected with 150 μCi ^{124}I-labeled PS (Reprinted with permission from Pandey et al. [178] Copyright (2009) American Chemical Society); (b) Schematic illustration of ^{64}Cu-radiolabel conjugation in PPF, microPET/CT images at 4, 24 h after intravenous injection of ^{64}Cu-PPF, tissue uptake of ^{64}Cu-PPF in some selected organs (Reprinted from Shi et al. [179] with permission from the Creative Commons (www.creativecommons.org)).

usually have sensitivity to light and can generate ROS. In vesicular NPs like niosomes and liposomes, this intra-bilayer ROS generation causes a fast degradation of NPs, thereby causing a jump in the release profile of all their hydrophobic/hydrophilic cargo. Our recent study on the *ex vivo* purging leukemic cancer cells from a tumor model shows that free OR141 leads to an anticancer immune response due to a photodynamic activation, which induces immunogenic cell death. This is due to the high tendency of OR141 to localize in the endoplasmic reticulum (ER), the oxidation of ER-associated proteins, the formation of high molecular weight complexes, and the inactivation of proteasomal deubiquitinases [215–218]. In contrast, OR141-loaded niosomes could cause another death path as well as immunogenic cell death and a significant cell growth inhibition due to permanent cell blebbing and cytoplasmic degradation. Moreover, another interesting idea for PDT purging is loading PSs into the bilayer of vesicular NPs to make them "photosensitive," which are typically interesting when a hydrophilic purging agent is loaded into the center of the liposome and can be released at a faster rate if subjected to proper irradiation [219–221]. Recently, photosensitive liposomes prepared by co-loading Protoporphyrin IX and DOX showed an effective eradication of MCF-7 tumor development in nude mice within 2 weeks due to the effect of the PS, which was used not only as a mixture of PDT and chemotherapy but also as "gates" in the liposomal bilayer to trigger the release of the chemo-agent [222].

9. Conclusion and Perspectives

In this review, we have provided a comprehensive account of the fascinating application of PDT for tissue purging, its current status, and some tips that should be considered in this regard. *Ex vivo* purging PDT can undoubtedly be employed as a promising strategy before clinical HSCT and OCT. However, primarily due to the restrictions of conventional PSs, it has not yet gained wide acceptance as a first-line treatment choice. Future studies on improving PSs for *ex vivo* procedures will also concentrate on absorption wavelengths and specificity enhancements.

Then, it can hopefully be expanded to employ for malignancy/viral purging or GVHD controlling in other transplantation types on various tissues. Despite the multiple benefits of PDT and significant development in this area, typical PSs are still far from optimal therapy for eradicating malignant cells from a tissue due to low permeability, non-specific phototoxicity, side effects, hydrophobicity, poor bioavailability, and self-aggregation tendency. Therefore, the application of NPs, which may enhance the biodistribution, prevent non-specific accumulation, cause EPR effect and increase bioavailability, is an extremely promising idea for future scientific breakthroughs. For this purpose, depending on the physiological characteristics of the targeted tumor, NPs should be designed and optimized by favoring specific size, surface charge, formulation materials, geometry, and surface modifications because their physicochemical properties can influence the success of the PDT. To sum up, the tissue PDT purging from malignancies is an exciting research area in its infancy. Therefore, before reaching clinical trials, it requires in-depth investigations of different PSs, PDT conditions, various NP types, and possible modifications.

Declaration of Competing Interest

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