Future of oncologic photodynamic therapy

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To shed light on the future of photodynamic therapy (PDT) requires rational analysis of the current state of the art. No doubt, future PDT will build on current clinical successes as well as an enhanced understanding of its mechanisms of action, which continue to be elucidated. The discovery of PDT is attributed to Oscar Raab who was employing dyes to study paramecia [1]. In addition to helping discover fluorescence phenomena from these dyes, Raab also noted that upon occasion the paramecia would succumb following intense illumination. This phenomenon was not lost on Raab or his professor von Tappenier who elucidated the oxygen-dependent nature of what he termed the photodynamic reaction (PDR) [2]. Thus, PDT was born through a serendipitous observation and by 1907 was an oncologic therapy option [3].

Despite this early success, PDT did not flourish, but did sporadically reappear in the clinical arena particularly in the late 1950s and early 1960s [4]. This work focused more on fluorescence detection [4–7]. In the 1970s Dougherty, who had completed a distinguished career in chemistry, began a second career in radiation biology studying radiation sensitizing chemicals. He joined a project already underway and was warned not to put the cell cultures near the windows when using select vital stains. When he asked why, he was told that the tumor cells would die when the added stain was exposed to light. Rather than following this advice, Dr Dougherty re-discovered PDT [8], and unlike those who came before, brought PDT to a worldwide audience by achieving regulatory approval, clinical indications and commercial production. For these efforts, he is honored as the father of PDT though, certainly, many members of this family exist.

**PDT in the clinic**

As currently practiced, PDT achieves lesion ablation due to light activation of an applied photosensitizing agent, which, when in the presence of oxygen, ultimately generates the PDR [9]. This reaction, based on the generation of reactive oxygen species, results in rapid cytotoxic and vasculotoxic shutdown, which has been demonstrated to be highly successful as a tumor-ablative therapy. The relative simplicity of drug activation by light leading to the PDR has allowed PDT to reach a worldwide audience. With several commercially available photosensitizing agents now on the market, numerous well designed clinical trials have demonstrated the efficacy of PDT on various cutaneous and deep tissue tumors. However, current photosensitizers and light sources still have a number of limitations. Future PDT will build on those findings to allow development and refinement of more optimal therapeutic agents and illumination devices. This article reviews the current state of the art and limitations of PDT, and highlight the progress being made towards the future of oncologic PDT.

**Photosensitizers**

The transfer of light energy is the basis of life on earth; therefore, it should come as little surprise that a myriad of naturally occurring as well as synthetic agents have this capacity [10]. When this transfer of light energy results in what is classically termed a type II oxidative reaction, the transfer agent is termed a photosensitizer (PS) (Figure 1). Very few PSs have been rigorously tested for clinical application and only
a handful have passed clinical trials to allow for regulatory approval for patient treatment. Furthermore, some PSs have passed regulatory approval in some countries, but not others, and are therefore unavailable for patients. This limited availability creates a significant impediment in the pathway to a potentially important oncologic intervention. It does the patient and practitioner little good to have potentially outstanding PSs that are not available when they are required.

Currently available PSs may have significantly different structures but most come from several inter-related families of dyes, porphyrins and chlorines [13]. These PSs share numerous clinical characteristics that allow for treatment success, but also have significant shortcomings, which when resolved through scientific advance, will bode well for future PDT. Currently, depending on the definitions of success, a clinically successful PS will have some or all of the following characteristics:

- Commercial availability
- Easily synthesized to allow for commercial production
- Synthetic purity for regulatory approval
- Amphility for tissue penetration
- Chemical stability for transport and reconstitution
- Concentration in target tissue
- Clearance from nontarget tissue
- No dark toxicity
- Clinically useful half-life in tissue
- Clinically useful activation energy and wavelength
- High quantum yield of triplet formation from the excited state
- High molar extinction coefficient
- Appropriate triplet lifetime to allow the triplet PS to interact with ground state triplet oxygen
- Various modes of application: topical, oral and intravenous

The difficulties in meeting these goals are myriad. From a pharmaceutical production standpoint, the ability to produce a stable drug that is identical from batch to batch and can be synthesized in a cost-effective manner is critical. For the patient, these concepts are irrelevant as what the end user requires is a relatively pain-free and effective therapy. For the scientist, the ability to determine the biological and physical effects may be pre-eminent. For the clinician, the need is for reliable clinical outcome with minimal short- and long-term morbidity. With these disparate requirements, it is a wonder that any drug can be successful, yet multiple PSs have passed muster via successful clinical trials, as will be highlighted. PSs that have been employed in oncology are shown in Table 1.

Currently, only the following PSs are widely available for oncologic indications and it is worthwhile to review how they fit into the current PDT paradigm.

**Photofrin®**

This is a proprietary mix of porphyrin monomers, dimers and oligomers, all of which are required for PDT activity in the patient [14]. This lack of synthetic purity would likely prevent Photofrin® (Axcan Pharma, Inc., QC, Canada) from achieving regulatory approval today. The drug can be synthesized in a cost-effective manner and is reconstituted under a wide variety of conditions allowing for use even in the developing world. It is not a very active PS, requiring prolonged treatment times (minutes to hours), though treatment itself is painless. The drug is delivered as an intravenous infusion, generally of 2.0 mg/kg, and PDT is initiated at 48 h post injection to allow for accumulation in target tissue and some
clearance from ‘normal’ tissue. Various wavelengths of light activate Photofrin, including 400 nm (blue light), 540 nm (green light) and 630 nm (red light). As red light may penetrate tissue to 1 cm depth, this is often employed for most clinical oncologic applications. However, significant PS accumulates in the skin, requiring approximately 6 weeks of photosensitivity precautions (i.e., avoidance of sunlight, room light is acceptable) meaning a significant lifestyle change for that period of time. Despite these shortcomings this PS has been available for two decades and has treated thousands of patients. It has achieved worldwide regulatory approval and was the basis of growth for oncologic PDT. The skin photosensitivity period and long treatment times have limited this PS, particularly in regions where other PSs have become available.

**Foscan®**

Foscan® is a highly active synthetic chlorin-based PS and treatment may require a minute or less [15]. In addition, the drug is so active that even room light may activate it, so patients must stay in a dimly lit room for approximately 24 h after intravenous introduction. A drug dose of 0.1 mg/kg and light of 652 nm is usually employed. In contrast to Photofrin, the treatment itself can be relatively painful. Furthermore, approximately 4 days post-infusion is required to achieve maximum differential in drug accumulation between tumor and normal tissue. Still, at the current drug dose/light dose little, if any, selectivity between normal and tumor tissue is seen. While widely available and widely used in Europe this PS did not achieve US FDA approval [12]. Despite this, Foscan has become the preferred PS to treat tumors of the head and neck, owing in large part to its rapid treatment time and shorter window of cutaneous photosensitivity (<2 weeks).

**Aminolevulinic acid**

Aminolevulinic acid (ALA) is a prodrug that is enzymatically converted to protoporphyrin IX, an active PS [16]. ALA may be introduced intravenously or orally, but has found great success in a topical form. This allows for highly specific PDT on areas of the skin placed in contact with the PS and eliminates generalized photosensitivity reactions. The PS itself is widely commercially available in various forms and is currently the PS frequently used for cutaneous applications [12]. The oral and intravenous forms have produced excellent outcomes for esophageal cancer, for example, but when delivered in this manner, may rarely result in gastrointestinal toxicity (nausea). As a topical formulation, tissue penetration is only several millimeters so blue light (400 nm) is used. For deeper penetration oral ALA (20 mg/kg) 3–4 h prior to PDT and red light are used. When taken orally, 72 h generalized skin photosensitivity is expected.

While these three PSs allow clinicians a limited choice, they also complement each other in terms of clinical indications. Clearly, much room for improvement exists for future PSs in PDT.

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**Table 1. Photosensitizers currently used in clinical oncology.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substance</th>
<th>Manufacturer</th>
<th>Ref.</th>
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<tr>
<td>Photofrin®</td>
<td>HpD</td>
<td>Axcan Pharma Inc. (QC, Canada)</td>
<td>[101]</td>
</tr>
<tr>
<td>Photogem®</td>
<td>HpD</td>
<td>Moscow Research Oncological Institute (Moscow, Russia)</td>
<td>[102]</td>
</tr>
<tr>
<td>Levulan®</td>
<td>ALA</td>
<td>DUSA Pharmaceuticals, Inc. (MA, USA)</td>
<td>[103]</td>
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<tr>
<td>Metvix®</td>
<td>M-ALA</td>
<td>PhotoCure ASA (Oslo, Norway)</td>
<td>[104]</td>
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<tr>
<td>Hexvix®</td>
<td>H-ALA</td>
<td>PhotoCure ASA</td>
<td>[105]</td>
</tr>
<tr>
<td>Visudyne®</td>
<td>Verteporfin</td>
<td>Novartis Pharmaceuticals (Basel, Switzerland)</td>
<td>[106]</td>
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<tr>
<td>Antrin®,</td>
<td>Lutexaphyrin</td>
<td>Pharmaclys (CA, USA)</td>
<td>[107]</td>
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<tr>
<td>Lu-Tex</td>
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<tr>
<td>Foscan®</td>
<td>Temoporfin</td>
<td>Biolitec Pharma Ltd (Dublin, Ireland)</td>
<td>[108]</td>
</tr>
<tr>
<td>LS11, Photolon®, Litx®, Aminolevulinic acid</td>
<td>Talaporf</td>
<td>Light Sciences (Washington DC, USA)</td>
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<td>Photochlor</td>
<td>HPPH</td>
<td>Roswell Park Cancer Institute (NY, USA)</td>
<td>[110]</td>
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<tr>
<td>Photosens®</td>
<td>Phthalocyanine</td>
<td>General Physics Institute (Moscow, Russia)</td>
<td>[111]</td>
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<td>Pc4</td>
<td>Phthalocyanine</td>
<td>Case Western Reserve University (OH, USA)</td>
<td>[112]</td>
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<tr>
<td>Tookad</td>
<td>Bacteriochlorophyll</td>
<td>The Weisman Institute of Science (Rehovot, Israel)</td>
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Light sources

With the introduction of laser light sources, more accurate and reproducible illumination became possible, as lasers could be tuned to the appropriate wavelength to activate a specific PS [17]. Furthermore, many of the commercially available lasers had built-in dosimetry tools, allowing the clinician to better calculate delivered light dose for more uniform and reproducible therapy. In addition, current lasers, particularly diode lasers, have become portable without the need for special cooling or electrical requirements, thus also improving access to PDT in developing regions of the world [11,18]. This technological advance allowed for unprecedented growth of PDT [19]. More recently, light-emitting diode (LED) light sources have become commercially available [17,19,20]. These are far less expensive than lasers, again allowing PDT to be brought to a worldwide audience in a more cost-effective manner. Of equal importance, fiber optics for lasers and flexible LEDs are now available, which can easily fit the apertures of endoscopes and biopsy needles; therefore, light can now routinely be brought into deep tissues via the bronchoscope, endoscope or through computed tomography-guided biopsy techniques, allowing for PDT of previously inaccessible tumors [21]. Prior to these advances, only the PS could reach these tumors, but the required illumination to activate the PS was not available. Now, with minimally invasive technology and illumination sources designed for these tools, a new frontier of PDT of deep tumors of the CNS [22], head and neck [23], thorax [24], and abdomen [25], among other anatomic regions [26], has developed.

Photodynamic reaction

The PDR is considered to be the successful creation of a type II redox reaction, which creates free radicals via singlet oxygen generation [27]. Therefore, PSs were chosen that favored this pathway of light activation. In reality, light energy can activate a PS in many ways (Figure 1) [28]. Another pathway occurs through a type I reaction. Here the light energy transfer results in target damage and ablation through a superoxide radical anion. Many PSs exist that allow for both type I and II pathway activation, making this use of these PSs advantageous. As tumors considered resistant to therapy are hypoxic, the use of direct toxicity (type III reaction) may be of clinical utility. A subtle point must be observed. As will be discussed, most current PS accumulates in membranes of cells and subcellular organelles. Therefore PDT appears to be nonmutagenic as it damages membranes, not DNA. By favoring a type III reaction one may actually create DNA damage and change PDT from a nonmutagenic treatment to a potentially mutagenic therapy. Two other clinically relevant pathways may also be activated by the introduction of light energy to the PS. One is fluorescence and the other in absence of oxygen is phosphorescence. Both produce visible light as the introduced light energy fades. Clinically, this can be exploited to allow for visualization of the tumor’s bed or extent. This may assist in demarcating tumor extent for PDT or for the surgeon’s knife [29]. This fluorescence phenomena may be used for photodiagnosis or optical biopsy, both of which are in their infancy [30]. Here, the difference between fluorescence/optical signal of tumor compared with normal tissue is exploited to assist in disease diagnosis.

Current clinical state of the art

Despite the limitations in PSs, light sources and the PDR, clinical PDT has continued to grow owing both to the simplicity of therapy and excellent clinical success, so it is worthwhile to analyze current clinical outcomes.

The topically applied PS, ALA and its related PS, methyl aminolevulinate (MAL) have found a growing niche in the treatment of cutaneous diseases [31]. As both ALA and MAL have very limited tissue penetration, PDT is limited to superficial lesions. In multiple well-designed clinical trials ALA and MAL PDT has been shown to eliminate actinic keratoses and superficial basal cell tumors quite effectively [32]. What has also been commented upon is the superior cosmetic outcomes patients achieve as compared with other forms of treatment such as curettage, freezing and other ablative techniques [33]. This superior cosmetic outcome forms a basis for PDT’s future use in dermatology. Similarly, ALA-based fluorescence and PDT hold great promise in the treatment of other superficial malignancies where functional outcome is critical, most notably for in situ bladder cancer where current therapies often ultimately result in the loss of this organ’s function [34]. ALA has also been used to assist in fluorescence guided resection. Both improved rates of clear margins and tighter resections sparing normal tissue are possible [35,36].
Foscan-based therapies have achieved excellent response for select primary and recurrent tumors of the head and neck [37]. Multiple trials report excellent tumor ablation for early stage head and neck primaries where risk of lymphatic metastasis is low (as PDT cannot yet treat the nodal chains). Significantly, PDT results in excellent functional preservation [38].

An important PDT trial also revealed excellent palliation for head and neck patients who failed surgery and radiation and had symptomatic local recurrence [39]. Most patients achieved an excellent level of symptom control and a minority had re-establishment of tumor control. As tumor control for head and neck cancer is tantamount to survival this was a great benefit. Similarly, Foscan demonstrates great potential for photodiagnosis and fluorescence-guided surgery in the brain [40].

Photofrin has been available for several decades and has a large body of literature reporting high tumor ablation rates with excellent functional outcomes [41]. Long-term data reveal its ability to preserve esophageal function with tumor elimination for primary esophageal tumors as well as Barrett’s esophagus [42,43]. A large head and neck population has achieved function-sparing therapy for early and obstructive lung cancers [45,46]. PDT allows for rapid tumor control with excellent functional preservation. Photofrin PDT has developed a niche for breast cancer patients with chest wall recurrence who have failed salvage surgery, radiation and chemotherapy [47,48]. Here, despite extensive prior therapy, tumor ablation with good wound healing is possible. Recently, Photofrin PDT has demonstrated a doubling of survival in randomized trials for patients with biliary cholangiocarcinoma [49-51]. Prolonged survival with a high quality of life is possible through outpatient treatment. The use of Photofrin in fluorescence-guided surgery and PDT have made great gains. Further progress has been made in treating CNS cancers, where the need for function-sparing surgery is critical [22,52].

While clinical outcomes can be excellent in terms of tumor control and functional preservation, clinical PDT therapy still has a number of relative shortcomings. With the exception of Photofrin, the actual treatment can be painful, which may prevent some patients from consenting. With the exception of topical ALA, sunlight restrictions may also prevent patients from choosing this therapy. The two-step stage of infusion and then waiting hours-to-days for the drug to accumulate into target tissue and clear from normal tissue makes it difficult to schedule actual treatment.

However, most difficult is the current lack of real time dosimetry [53,54]. Dosimetry is the means to optimize therapeutic outcome and minimize normal tissue effects [55]. In contrast to light dosimetry, radiation dosimetry has been well worked out, resulting in dramatic improvement in radiotherapy. No such improvement has yet been seen for PDT, so clinically, a significant acute tissue reaction generally occurs during the actual PDT sessions for both tumor and surrounding normal tissue. While possibly of limited consequence for PDT of the skin, this can lead to obstruction of the airway following PDT of the lungs. More accurate dosimetry to minimize acute normal tissue reactions and enhance long-term normal tissue healing is the key to future dosimetry for PDT. The combination of these shortcomings has limited the growth of PDT.

Of consequence too, is the fact that surgery and radiation therapy, the two standard choices for local tumor control, have dramatically improved technology (e.g., robotics and radio surgery) so that minimally invasive, highly functional outcomes with these treatments are much more common today than even a decade ago. As minimally invasive and functional sparing was a key component of the original argument for introducing PDT to the clinic over conventional surgery and radiation, this argument has been weakened, albeit only in countries with highly developed medical infrastructure.

**Future PDT**

The future of PDT will require a reanalysis of what a PS is, what a light source is and what can be done to manipulate the PDR. Today the practitioner of PDT employs tools quite similar to those of PDT pioneers and delivers therapy in a fashion not much different than that offered 100 years ago. It is doubtful that the same will be said even by the end of this decade.

**Future PSs**

The current group of PSs accumulate in target tissue for reasons that remain unclear but can be attributed to various receptors and the microenvironment of tumors [56]. Clearing of PS is thought to be based on improved circulation...
in normal tissue compared with tumors \([57]\). To improve selectivity this paradigm must be fully elucidated and manipulated.

Currently, it is believed that most PSs travel intravenously as complexes of serum proteins \([58]\). At this small size they may not generally be recognized by the reticulo-endothelial system, though PS may still undergo uptake by the Kupfer cells of the liver. The PSs are then taken up preferentially by rapidly proliferating tissue, such as tumor tissue. This may be through a mechanism similar or identical to the low-density lipoprotein receptor. Leaky neovascularure will also allow for enhanced permeability and accumulation of the PS in the tumor region. Designing future PSs to bind to tumor-specific receptors or by conjugating PSs to compounds that bind to these regions are fertile means to improve PS specificity. Other areas of exploration include localizing PSs to hypoxic regions, which are considered relatively resistant to current therapy, and altering the PS so that it may directly involve the immune system rather than avoiding it as current intact PSs seems to do \([59,60]\).

The current group of PSs can be further exploited to improve both future PDT and oncologic therapy through their ability to image tumors and by combining the PS with additional therapeutic agents.

**Imaging**

The structure of current PSs is similar to contrast agents used in radiology so it would not be out of the question to use current PSs as both diagnostic and therapeutic agents \([61]\). The PS could be employed to better define tumor beds through its imaging characteristics, and then assist in ablation via PDT. Imaging could be by anatomic localization for computerized axial tomography scanning or MRI, or in a more ingenious fashion via biologic imaging. If PSs were designed to accumulate in hypoxic regions this could be a means to better define hypoxic areas of tumors that may require additional therapy. Furthermore, changes in PS activity could be used as a means of determining treatment success or failure, which will be discussed later \([62]\). The fluorescence capability of most PSs is under-utilized and could be employed to assist in improving treatment targeting or even delineation of margin status for surgery \([63]\). It should be noted that PDT and fluorescence are competing pathways, so highly efficient fluoro-rescing agents may be poor PSs and vice versa. Fluorescence-guided surgery may better allow the surgeon to spare normal tissue and achieve clear tumor margins. This has already been demonstrated to be feasible for cutaneous tumors and bladder cancer \([64,65]\). Current PSs may also be employed as a one-two punch against tumors, using both surgery to remove gross disease and PDT to eliminate microscopic extensions.

**Conjugating**

Conjugating current PSs is another means to improve outcomes \([66–68]\). The conjugate may be radioactive for additional tumor destruction, or act as a tag to have an additional means to detect cellular function and turn pathways on or off. This would have both clinical and scientific implications. A particularly promising conjugate is based on a PS attached to a chemotherapeutic agent. The PS and chemotherapeutic agents accumulate in the tumor membrane and via illumination lead to PDT as well as release (photolysis) of the chemotherapeutic agent \([69,70]\). The conjugates might be an antibody, imaging agent, or perhaps most exciting, a nanoparticle.

**Nanoparticles**

Nanoparticles are likely to represent the next generation of PSs \([58]\). Current PSs require amphility, the ability both to travel unhindered through the blood system and then to localize and be introduced into the target tissue. While several of the current PSs may have this ability, many other potentially outstanding PS agents lack either the ability to readily travel through the body or to be concentrated appropriately at the target. This is one area where nanoparticles will play an important role. By encapsulating current PSs within well-designed nanoparticles, the ability to traverse the body intravenously will become possible. Furthermore, this will allow for precise localization at specific sites within the tumor or neovascularure. Therefore, chemists will be able to synthesize highly efficient PS agents that previously could not be used owing to issues such as hydrophobicity, lipophobicity, clumping, non-target toxicity and dark toxicity among numerous other inappropriate characteristics of current agents \([71]\). The nanoparticle would not only be used for targeted transport but also to prevent PS from concentrating, for example, in skin. In reality the biological and physical activity of the PS would be controlled via the nanoparticles, so tissue half-life and other characteristics would be based on the designed nanoparticles rather than the variability associated with current PSs.
The nanoparticle could be created to bring the PS to very specific sites within tumors through a variety of techniques. This may also assist in better defining the oncologic process, perhaps ultimately creating an on–off switch to reverse malignant changes [72].

One may even create paramagnetic PS nanoparticles that would be directed to tumors by magnetic means [73]. The magnetic field could also be used to heat the tumor via hyperthermia of the nanoparticles in addition to light illumination via PDT. Future PS–nanoparticles conjugates may play a myriad of diagnostic and therapeutic roles. These may include fluorescing in the presence of a particular protein, toxin or even malignant cell. If designed appropriately, the PS would then be activated to destroy the offending target.

**Light sources**

As light sources have miniaturized and become portable, PDT has expanded. With the continuing dramatic advances in light production, this aspect of PDT will become highly refined (Figure 2) [17,21,74]. While lasers have remained the mainstay for much of PDT they are expensive and still relatively large. By contrast, LED technology has come to the forefront of PDT. These tiny and often battery-operated light sources can now easily fit through scopes and biopsy channels for deep tissue illumination. They can also be designed for easy surface illumination through various arrays. The advance here is the highly portable energy source, for example, battery power, which is self contained. Now the patient can be mobile during illumination. This allows for the realization of prolonged outpatient illumination as well as metronomic repeated illumination [75]. Originally, PDT developed as a single intense illumination session, mainly because it was difficult to illuminate repeatedly, particularly for deep lesions. It is well known from most radiotherapy and chemotherapy protocols that fractionation of dose delivery may allow for excellent tumor control and diminished normal tissue damage. Therefore, the new ability for prolonged light and multiple fractions of illumination may further improve PDT outcomes or normal tissue recovery [76]. Even more impressive is the development of organic LED technology (Figure 3) [58]. These light sources can be made from films that could be implanted to cover an entire tumor, opening new and innovative illumination pathways. Ultimately, dissolvable light sources with built-in timers that turn on and off when in contact with the PS could be created, which would be a truly fantastic means to offer future PDT. This may be possible based on nanoparticle light sources.

Conceivably, a PS–light source conjugate could also be created. Illumination could be started upon contact with tumor or through additional energy brought in via magnets (MRI), heat or radiation from other energy sources.

**Figure 2.** An implantable light source for prolonged or metronomic photodynamic therapy (Light Science Oncology [109]). Reproduced with permission from [21].

**Figure 3.** A possible future light source of flexible and film-like material composed of organic light emitting diodes. Reproduced with permission from [114].
Here, highly accurate localization of treatment would also be possible through two-photon technology [77]. What is notable in this situation is that the PS and light source are so close together that shorter wavelengths of light, which travel only a few millimeters, could be used to activate the PS. This is in contrast to today’s PSs, which use longer wavelengths of light, which, owing to deeper tissue penetration, may cause unneeded PDT in tissue centimeters from the target. The future use of shorter light wavelength could allow for far less collateral damage to normal tissue regions that should not be illuminated.

### Photodynamic reaction

As mentioned, current PSs favor a type II pathway, but the other pathways (type I, fluorescence and so on) remain an underutilized avenue to improve PDT. Future PDT will also likely better exploit the location of the PDR. Achieving PDR exclusively in vessels will allow for vascular shutdown [78]. Tumor cell PDR may allow for apoptotic response and/or necrosis [59]. In the future these locations will be better controlled depending on the specific clinical situation. More specific localization of the PDR onto specific subcellular membranes such as mitochondria may also influence the type of clinical outcomes seen with PDT, an area of active exploration [9]. Release of cytokines may allow for immune response via select tumor-destructive pathways, resulting in a systemic immune response [79]. Thus PDT-based vaccines using antigen presentation and cytokine release are distinct possibilities for the future [80]. By modulating the PDR, one may also prevent immune stimulation when indicated.

It would not seem unreasonable that the PDR could be used for tissue regeneration instead of ablation [81]. The outstanding cosmetic outcomes from PDT may well result from this. Furthermore, the combination of fluorescence and PDR can be used to study the steps in the oncologic process and development of metastasis. As stem cells appear to be involved in tumorigenesis and healing, we may be able to use both PDR and PDT to better define these complex cells and their differentiation pathways and processes. Conceivably too, with nanoparticles, quenchers of the PDR could be created to further define regions for protection instead of regions for treatment. Real-time dosimetry may well be achieved via nanoparticle dosimeters, which would turn the PDR off when the tumor was ablated, similar in concept to nanoparticle-based labs on a chip, which can accurately determine the presence of malignant cells, among other possibilities.

### Future perspective

The future direction of scientific PDT will no doubt include the delineation of accurate and individualized therapy through improved PS agents, which may be enhanced through nanoparticles and conjugates, innovative light sources and better control of the PDR. These tools will also allow for better definition and understanding of the immune system and stem cells not only in terms of tumorigenesis but also in terms of healing.

The future direction of clinical PDT will require the availability of PS and tools for treatment, which is not guaranteed. Most PDT companies are relatively small, so this is of great concern. Fortunately, some governments have seen the value of PDT in terms of cost-effectiveness and have made the future of clinical PDT more reliable [11,18,82]. It has become clear that PDT offers excellent function-sparing tumor ablation therapy without the need for expensive investment in surgical suites, robots, high-end linear accelerators and other such devices. This has allowed for unprecedented growth of PDT in, for example, Brazil [11]. While PDT was designed for tumor ablation it has also found use in dermatology not only for therapy of superficial malignancies but now more often for outstanding cosmetic purposes and facial rejuvenation. This regeneration of skin may form the basis not only for wound healing but perhaps for tissue and organ regeneration. The burgeoning exploration of PDT as an immune modulator may find this clinical application growing in immunotherapy and vaccination. The ability to destroy plaques and neovasculature will become common.

Furthermore, as the PDR is not limited to tumors [83], one will see PDT growing as a means of antimicrobial therapy, antiviral therapy and antifungal therapy; perhaps even as a means to sterilize microorganisms that cause food-borne illness and also to bind and destroy poisons. While developed heavily as an oncologic intervention, PDT has now grown far beyond this indication, which may be looked back on as a fundamental stepping stone to a myriad of other uses.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Executive summary

Current photodynamic therapy

- Photodynamic therapy (PDT) is a tumor ablative, yet function-sparing oncologic therapy.
- PDT consists of an applied photosensitizing agent that, when activated by the appropriate intensity and wavelength of light, leads to the cytotoxic and vascular toxic photodynamic reaction (PDR).
- Photosensitizing agents may be natural or synthetic.
- Currently available photosensitizer (PS) agents are dyes, porphyrins or chlorines.
- While many PSs exist or can be created, few have been employed in clinical trials and even fewer are commercially available.
- Successful PS agents are easily synthesized, stable, nontoxic until activated by light, concentrate to a degree in tumors, clear normal tissue and allow for reliable tumor ablation.
- All commercially available PS have drawbacks, including normal skin photosensitivity, prolonged treatment times and pain on illumination.
- Light sources are required to activate the PS.
- Each PS has a unique light wavelength and intensity requirement.
- Lasers and light emitting diodes are commercially available to activate each PS.
- Sunlight is a broad spectrum, intense light source that can inadvertently activate the PS in sunlight-exposed anatomy, so photosensitivity precautions are critical.
- Optic fibers allow light sources to be brought to virtually any tissue.
- When a PS is activated by light the PDR may occur.
- The PDR is a type II reaction that generates highly toxic singlet oxygen species.
- As PSs generally accumulate in cell membranes, the PDR occurs here.
- Despite the shortcomings of currently available PSs and light sources, PDT has demonstrated an excellent effect in a variety of tumors of the skin, head and neck, lung, esophagus, breast and other tumor sites.
- PDT for cholangiocarcinoma has doubled patient survival times.

Future PDT

- The current generation of PSs can be better employed.
- This includes their use as imaging tools as well as cytotoxic tools.
- Current PSs have fluorescence capability, which allows for tumor demarcation, assisting the surgeon.
- The use of fluorescence and PDT will improve tumor targeting.
- Changes in fluorescence may be a means to improve treatment dosimetry as well as accuracy.
- Future PS agents may be designed for specific receptors.
- Future PSs may be encapsulated by nanoparticles (NPs) to improve targeting and tissue penetration.
- NP–PS conjugates that also allow for imaging as well as therapy may be synthesized.
- NP–PS may, for example, be paramagnetic. This would allow MRI imaging and magnetic fields to direct the NP to the tumor. In addition to PDT, the magnets could heat the NP to allow for hyperthermia.
- Future light sources will be miniaturized.
- These miniature light sources will be implantable for prolonged illumination and metronomic therapy.
- Implantable and dissolvable organic light emitting diode light sources with built-in timers will be created that conform to tumor beds.
- NPs may serve as the light source.
- NPs could be turned on or off by external energy supplies such as magnetic fields or radiation.
- The PDR will be better controlled in the future with greater ability to limit this to tumor beds.
- By controlling the PDR, one may favor apoptosis with a truly local response or necrosis with release of cytotines resulting in an immune response.
- PDT-based vaccination will become possible.
- As PDT offers excellent wound healing, exploiting this pathway may generate tissue regenerative approaches.
- Stem cells may be tagged by PS, and the pathways for tumor genesis as well as healing will become clearer through fluorescence imaging.
- PDT of the future will include the treatment of nonmalignancies, such as bacterial, viral and fungal infections.
- Future PDT will include emphasis on cutaneous rejuvenation and elimination, for example, of unwanted tissue such as plaque, neovasculature, scar and fibrosis.
Perspective

Allison, Bagnato & Sibata

Bibliography

Papers of special note have been highlighted as:
• of interest
** of considerable interest
• Overview of clinical outcomes in oncology.
** Classic article introducing aminolevulinic acid-based photodynamic therapy (PDT).
** Excellent overview of PDT in oncology.

• Review and examination of nanotechnology and its application to PDT.


**Excellent outline of PDT in oncology.**


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