Photosensitizers in clinical PDT

Ron R Allison, MD\textsuperscript{a,b,*}, Gordon H Downie, MD, PhD\textsuperscript{b,c}, Rosa Cuenca, MD\textsuperscript{d}, Xin-Hua Hu, PhD\textsuperscript{a,b,e}, Carter JH Childs, MD\textsuperscript{b,c}, Claudio H Sibata, PhD\textsuperscript{a,b,e}

\textsuperscript{a} Department of Radiation Oncology, Brody School of Medicine, East Carolina University, Greenville, NC 27858, USA
\textsuperscript{b} PDT Center, Leo Jenkins Cancer Center, Brody School of Medicine, East Carolina University, Greenville, NC 27858, USA
\textsuperscript{c} Department of Medicine, Pulmonary and Critical Care Medicine, Brody School of Medicine, East Carolina University, Greenville, NC 27858, USA
\textsuperscript{d} Department of Surgical Oncology, Brody School of Medicine, East Carolina University, Greenville, NC 27858, USA
\textsuperscript{e} Department of Physics, East Carolina University, Greenville, NC 27858, USA

KEYWORDS Photosensitizers; Photodynamic therapy; Review

Summary Photosensitizers in photodynamic therapy allow for the transfer and translation of light energy into a type II chemical reaction. In clinical practice, photosensitizers arise from three families—porphyrins, chlorophylls, and dyes. All clinically successful photosensitizers have the ability to a greater or lesser degree, to target specific tissues or their vasculature to achieve ablation. Each photosensitizer needs to reliably activate at a high enough light wavelength useful for therapy. Their ability to fluoresce and visualize the lesion is a bonus. Photosensitizers developed from each family have unique properties that have so far been minimally clinically exploited. This review looks at the potential benefits and consequences of each major photosensitizer that has been tried in a clinical setting.

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Historical perspectives

Treatment using light and light activated compounds are referenced in ancient times, and were used to treat a wide variety of disorders and malaise [1–3]. Of particular note were salves placed on cutaneous tumors that were then exposed to sunlight with good response. The 1903 Nobel Prize was awarded to Niels Finsen for his work on phototherapy. Finsen discovered that light treatment could control skin manifestations of tuberculosis, a very common ailment at that time [4]. Similarly light could successfully treat other significant medical conditions such as rickets and neonatal-hyperbilirubinemia. The use of an added
chemical photosensitizer, rather than a natural chromophore, developed from progressively more elegant studies by Raab [5] and Jesionek and Von Tappeiner [6]. In Raab’s initial work adding dyes to petri dishes of paramecia resulted in unexplained death during daylight experiments, but not during evening experiments. Rather than ignoring these findings Raab systematically proved the connection between light activation of these dyes and therapeuthic outcome. Continued work revealed the basis for the oxygen- and light-dependent photodynamic reaction and resulted in the coining of this important term [7,8]. Interestingly, but not surprisingly, at the same time clinical cases of porphyreus were widely described with their inherent photosensitivity and its consequences. The fundamental basis for the disease was elucidated as an excess of porphyrins [9]. For the most part these clinical and scientific findings were considered oddities until the 1970s when Dougherty, like Raab, serendipitously placed radiation sensitizing agents in cell culture near lab windows and noted significant cell death. Rather than taking the advice of his co-workers to keep the cultures out of the light, Dougherty isolated and studied the agent responsible for this successful failure, which was none other than a porphyrin [10,11].

### Ideal photosensitizers

In order to critique clinically available photosensitizers, one must have some sort of ideal for comparison. However, the ideal photosensitizer would vary from clinicians to purists. We believe the guidelines that follow are clinically relevant.

### Guidelines

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td>One does not want a toxic chemical, otherwise chemotherapeutic agents could be used. Further, metabolicism of the photosensitizer should not create new toxic byproducts.</td>
</tr>
<tr>
<td>2</td>
<td>Mutagenicity/carcinogenicity</td>
</tr>
<tr>
<td></td>
<td>The photosensitizer should not cure one disease only to create another.</td>
</tr>
<tr>
<td>3</td>
<td>Elimination</td>
</tr>
<tr>
<td></td>
<td>Removal of the photosensitizer from the patient should be of clinical utility. One may want to retreat a patient without re-administering the photosensitizer, so half-life may be of consequence.</td>
</tr>
<tr>
<td>4</td>
<td>Selectivity/targetability</td>
</tr>
<tr>
<td></td>
<td>A photosensitizer that goes where you want it to go and accumulates selectively in those tissues can be beneficial. This assumes that one understands the correct target for illumination and activation. Intracellular targets, such as mitochondrial membranes, will lead to intracellular programed death by apoptosis. Cell membrane or extra cellular-based death via vessel collapse will lead to necrosis. Necrosis initiates the cytokine family of response with systemic consequences. Clearly, the target of destruction can be important and have clinical consequences. One may be able to exploit this to create PDT vaccines via encouraging systemic response or avoid this by highly selective apoptotic response [12]. Additionally, one could conjugate the photosensitizer, for example, to carriers, monoclonal antibodies, radioactive source, etc. to enhance specificity and destructive capability. However, these “advances” contain their own new side effects.</td>
</tr>
<tr>
<td>5</td>
<td>Activation</td>
</tr>
<tr>
<td></td>
<td>Reliable activation by an appropriate wavelength of light is needed to prevent accidental treatment.</td>
</tr>
<tr>
<td>6</td>
<td>Sunlight precautions</td>
</tr>
<tr>
<td></td>
<td>As all photosensitizers go to skin, some degree of sunlight precautions are needed. Ideally, this would be measured in hours or days and not weeks or months.</td>
</tr>
<tr>
<td>7</td>
<td>Administration</td>
</tr>
<tr>
<td></td>
<td>Versatile by topical, swallowing, inhalation or IV, depending on the clinical situation. In any case, minimal administrative toxicity (i.e. hypotension, allergic reaction) and ease of administration are valuable characteristics.</td>
</tr>
</tbody>
</table>
### Photosensitizers in clinical PDT

(8) **Indications**
Will it be better to have very specific drugs for specific medical indications (i.e. a family of photosensitizers with specific indications) or one drug that works on most diseases?

(9) **Reliability**
Even the best theoretical photosensitizer must get where you need it and activate when you need it, each and every time, or it is almost useless.

(10) **Pain-free therapy**
Since PDT is done as an outpatient and does not usually need sedation, a photosensitizer that induces pain during and after therapy will not allow for successful outpatient PDT.

(11) **Outpatient therapy**
Outpatient administration and therapy is patient friendly. It is also cost effective. As therapy costs play a greater role in insurance decisions, keeping PDT less costly than other modalities is important. Patients also prefer outpatient care over hospitalization.

(12) **Availability**
The photosensitizer must be commercially available and able to be reconstituted by a local pharmacy rather than sub specialty labs.

(13) **Cost**
A prohibitively expensive drug will prevent its wide use.

(14) **Safety**
Ideally you want to be able to give this photosensitizer without significant worry and feel that when therapy is initiated good clinical outcomes will occur. You do not want the photosensitizer to induce morbidity such as clots, stroke, heart attack, etc.

(15) **Biochemistry**
Water-soluble photosensitizers easily travel the body. With chemical manipulation non-soluble photosensitizers can be synthesized with appropriate carriers to allow for clinical use.

(16) **Wavelength**
Longer wavelengths of activation allow for deeper tissue penetration. Activation at 400 nm is measured at a millimeter light depth penetration; 630 nm gives about 10 mm depth. This assumes light penetrates similarly between normal and tumor tissue, which clinically it does not.

(17) **Integrative ability**
An optimal photosensitizer will be able to be used in conjunction with other forms of treatment such as surgery, radiation, and chemotherapy. A photosensitizer that prevents use of these modalities will not be clinically successful.

(18) **Forgiving**
With limited dosimetry available highly active photosensitizers may easily permit treatment overdosage. Less active photosensitizers may be more forgiving of excess illumination.

(19) **Transparency**
The ideal photosensitizer would be easily and safely administered, target the appropriate structure, avoid normal tissues, activate when needed until the structure in question is destroyed and then eliminate itself without causing permanent damage to the rest of the body. It would also tell you that you were successful and help you to achieve success if you were not.

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**Fluorescence**

Having a photosensitizer assist in therapy is an important concept. Light energy brought to the photosensitizer can go through several distinct pathways. For therapy, one wants the pathway that creates a photodynamic reaction although other pathways can be clinically useful. A pathway for fluorescence is extremely beneficial. Employing fluorescence one can define and adjust the treatment fields. The tumor bed will light up, as will other regions containing malignant cells. This could easily direct the light fields and cause modification or additional light fields required for therapy [13]. Further, fluorescent spectra may differentiate benign and malignant regions and prevent therapy to normal tissues [14]. The fluorescent signature can also be used as an optical biopsy to determine benign versus malignant disease without the need for histological evaluation [15,16]. Finally, one can imagine that the difference in fluorescence prior, during, and after therapy could be used to evaluate the potential success or failure of treatment [17]. Of particular interest is the change in fluorescence during therapy which may be an excellent dosimetric guide to modification of illumination [13,18]. Clearly, fluorescence should be considered a key necessity for a successful photosensitizer. However, the sum of fluorescence and PDT is unity, so the more powerful a fluorescent
marker, the less active the PDT agent and vice versa [2].

Dosimetry

Dosimetry is an alien concept to most clinicians. However, dosimetry is the single most important and least understood aspect of photodynamic therapy in general and photosensitizers in particular. While this paper’s focus is on clinical photosensitizers, dosimetry truly is the alpha and omega of PDT. Dosimetry allows for a homogeneous or non-homogeneous dose distribution over the region requiring PDT and also evaluates in a quantitative fashion dosing of normal tissues. Clearly, the ideal light dose cloud for PDT would produce lethal effects over the malignant region while minimizing damage to normal regions. In other words, enough light of appropriate absorbed photon density would three dimensionally cover the tumor bed, allowing successful PDT. Unfortunately, no such real time dosimetry system exists. Clinicians are left with guesswork on treatment parameters based on drug dose and administered light illumination fluence at the tissue interface, neither of which are accurate parameters to predict actual light distribution in any patient. PDT dosimetry is currently at the stage where radiation dosimetry was over 100 years ago. Old time radiation therapists were able to treat many tumors based on crude equivalents of time and radioactive source strength. Amazingly, successes occurred, but at high cost to normal tissue. It appears that PDT is following the same course. Until real time accurate dosimetry is developed for PDT not even the most promising photosensitizer will ever reach potential.

This lack of control has significant clinical ramifications. Without proper dosimetry one cannot explain failures resulting from a lack of proper amount of photosensitizer, light or oxygen. Overtreatment leads to side effects; undertreatment to failure. This lack of accurate dosimetry and the clinician’s lack of understanding of its ramifications will unfortunately hold back PDT; for example, with our current knowledge, significant normal tissue reaction in the airway and esophagus are taken as normal and expected when, in reality, with appropriate dosimetry these common and expected morbidities might be avoidable. This necessitates a very forgiving photosensitizer based on light overdosage.

Some work has been done in this area and as a prelude to the long-term goal of developing accurate modeling tools and quantitative planning systems for clinical PDT, our group has established a quantitative PDT model which combines Monte Carlo-based light dosimetry calculations with a group of rate equations to understand the PDT complex process [19]. In this model the realistic case of tumor embedded in normal tissue was simulated with a heterogeneous phantom to derive the 3D light distribution inside and outside the embedded tumor within the framework of the radiative transfer theory. The photodynamic reaction problem is solved in the time domain based on a set of rate equations first proposed by Foster et al. [20]. With this model, we were able to define the decay times of photosensitizer and unoxidized intracellular receptors to quantitatively describe the photobleaching effect and cytotoxicity of PDT, respectively, as a function of photosensitizer dose and photon density distribution.

Clinical photosensitizers

Many products can behave as photosensitizers and new ones are regularly discovered; however, very few have made it to clinical trial and even fewer are readily commercially available. We will examine the photosensitizers on the market, based on published peer-reviewed papers. Table 1 lists the currently available photosensitizers.

Table 1: Currently available photosensitizers.

<table>
<thead>
<tr>
<th>Platform</th>
<th>Drug</th>
<th>Substance</th>
<th>Manufacturer</th>
<th>Web site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyrin</td>
<td>Photofrin®</td>
<td>HpD</td>
<td>Axicam Pharma, Inc.</td>
<td><a href="http://www.axcan.com">www.axcan.com</a></td>
</tr>
<tr>
<td>Porphyrin</td>
<td>Levulan®</td>
<td>ALA</td>
<td>DUSA Pharmaceuticals, Inc.</td>
<td><a href="http://www.dusapharma.com">www.dusapharma.com</a></td>
</tr>
<tr>
<td>Porphyrin</td>
<td>Metvix®</td>
<td>M-ALA</td>
<td>PhotoCure ASA</td>
<td><a href="http://www.photocure.com">www.photocure.com</a></td>
</tr>
<tr>
<td>Porphyrin</td>
<td>Visudyne®</td>
<td>Verteporfin</td>
<td>Novartis Pharmaceuticals</td>
<td><a href="http://www.visudyne.com">www.visudyne.com</a></td>
</tr>
<tr>
<td>Tetraphyrin</td>
<td>Antrin®</td>
<td>Luxetaphyrin</td>
<td>Pharmacies</td>
<td><a href="http://www.pharmacies.com">www.pharmacies.com</a></td>
</tr>
<tr>
<td>Chlorin</td>
<td>Foscan®</td>
<td>Temoporfin</td>
<td>Biolyte Pharma Ltd.</td>
<td><a href="http://www.biolytepharma.com">www.biolytepharma.com</a></td>
</tr>
<tr>
<td>Chlorin</td>
<td>LS11</td>
<td>Talaporfin</td>
<td>Light Science</td>
<td><a href="http://www.lightsciences.com">www.lightsciences.com</a></td>
</tr>
<tr>
<td>Chlorin</td>
<td>Photochlor</td>
<td>HPHPH</td>
<td>RPCI</td>
<td><a href="http://www.rpci.com">www.rpci.com</a></td>
</tr>
<tr>
<td>Dye</td>
<td>Photosens®</td>
<td>Phthalocyanine</td>
<td>General Physics Institute</td>
<td><a href="http://www.gpi.ru">www.gpi.ru</a></td>
</tr>
</tbody>
</table>
current clinical photosensitizers and their manufacturers.

**Photosensitizing families**

Photosensitizers can be categorized by direct chemical structure and come from several broad families. Table 2 outlines the photosensitizers families discussed in this review. The first family discovered is based on hematoporphyrin (Hp) and its derivatives. After purification and manipulation hematoporphyrin derivative (HpD) is transformed into commercial products variously called Photofrin®, Photosan, Photocan, etc. [21]. These products are composed of differing fractions of porphyrin monomers, dimers, and oligomers which are required for successful therapy [22]. Depending on the purification steps these commercial products may not be identical, though clinically, they appear equivalent [23]. However, this statement must be made with extreme caution. By adding, subtracting or substituting structures on the porphyrin ring, additional photosensitizers can be created. For example, m-THPP, with chemical substitutions, appears more potent as do sulphonated derivatives such as TPPS4, though toxicity unrelated to PDT is possible with systemic use of these agents [24]. As an example, TPPS4 was found to be neurotoxic on systemic administration [25]; however, with topical use, perhaps due to lower concentration of photosensitizer, no neurotoxicity was seen [26]. Yet topical application led to inhomogeneous distribution in tumors and lack of reliable response. Verteporfin is a benzoporphyrin derivative of porphyrin that is highly clinically active [27]. Interestingly, with knowledge of the heme synthetic pathway, one can exploit the endogenous photosensitizer protoporphyrin [28]. The prodrug δ-aminolevulinic acid when administered, even topically, will alter the natural heme synthesis feedback loop to create enough excess protoporphyrin for clinical utility.

Not to be outdone, mother nature has given us the magnificent series of chemical events called photosynthesis [1,29]. Clearly, light energy is well used in this process. Chlorophyll like substances termed chlorines have excellent photosensitizing properties as expected [30]. Multiple drugs have been created with some commercially available. These include modifications of chlorophyll and chemically synthesized structures. Clinically relevant photosensitizers are m-THPC [31], MACE [32], and NpE6 [33]. Purins, degradation products of chlorophyll, also are relevant. This is exemplified by the purpurin SNET2 [34]. Certain bacteria and algae have chlorophyll like activity such as the bacteriochlorins MTHPBC [35]. Looking back to the days of Raab, dyes remain a fertile ground to develop successful photosensitizers. Phthalocyanine dyes appear to have great potential, as do Naphthalocyanines [30,36].

**The generation gap**

The porphyrins are generally called first generation photosensitizers. Sometimes first generation labels photosensitizers developed in the 1970s and early 1980s, which by the way are the porphyrins. Second generation photosensitizers refer more to porphyrin derivatives or synthetics made from the late 1980s on. Third generation photosensitizers take available drugs and then modify them with antibody conjugates, built in photo bleaching capability, biologic conjugates, etc. [37]. Dividing drugs into generations wrongly implies that newer drugs are better than older drugs. Since the newer drugs still have photosensitivity, often gave pain during injection, treatment, and follow-up, are less specific and active than their bio-chemical profile would predict, seem to penetrate to depths no different than what first generation drugs do, and, in fact, may be less safe to use clinically than older drugs, one must be extremely cautious in their use. Further as most reports on newer drugs are presented in abstract form on very limited numbers of patients with extremely limited follow-up, caution remains the name of the game. Until head to head comparisons of different photosensitizers, in large multi-institutional studies, with appropriate dosimetric considerations, as well as unbiased interpretation of results are published, the claim that newer photosensitizers are “better” than older ones is unjustified. Patients who have been through surgery, radiation, and multiple chemotherapy agents are fully aware that 30 days of sunlight photosensitivity is a small price to

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**Table 2 Photosensitizer families.**

<table>
<thead>
<tr>
<th>Porphyrin platform</th>
<th>Hp (hematoporphyrin derivative)</th>
<th>HpD-based</th>
<th>BPD (benzoporphyrin derivative)</th>
<th>ALA (δ-aminolevulinic acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorophyll platform</td>
<td>Chlorins</td>
<td>Purpurins</td>
<td>Bacteriochlorins</td>
<td>Dyes</td>
</tr>
<tr>
<td></td>
<td>Phthalocyanine</td>
<td>Naphthalocyanine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
pay for reliable and painless photodynamic therapy. Patients who are unwilling to avoid sunlight precautions for 30 days are going to be the same patients who will not stay out of the light for 3, 7, or 10 days. These are the specific patients who should not readily be offered photodynamic therapy because they will not comply to the light restrictions.

Porphyrin family

Hematoporphyrin derivative (HpD)

Photofrin® (HpD) is commercially available from Axcan Pharma, Inc. and has the longest clinical history and patient track record. Fig. 1 shows the molecular structure for Photofrin®. The photosensitizer is actually a proprietary combination of monomers, dimers, and oligomers derived from chemical manipulation of hematoporphyrin [38]. The complex mixture is required for clinical activity. Similarly named photosensitizers derived by similar or different means from hematoporphyrins are also available from different groups in different parts of the world [39]. Under no circumstances should one assume the clinical activities are interchangeable. In the US, Photofrin® is FDA approved for early and late endobronchial lesions as well as Barrett’s esophagus and obstructing esophageal lesions [46–57]. Locally recurrent tumors of the rectum and anus can also be successfully treated [58,59]. Promising results have been seen in brain tumors [60–62] as well as head and neck neoplasms [63]. Bladder tumors are also responsive [64].

In general Photofrin® is infused at 2 mg/kg in an outpatient setting. About 48h later illumination occurs generally by a diffusing fiber (which illuminates in a circumferential manner) or more rarely by a micro lens (which is unidirectional). Depending on the clinical situation light dose of 150 J/cm² (lens) or 200–300 J/cm (diffuser) is employed. The clinical results are generally excellent. A wide variety of cutaneous lesions including squamous cell, basal cell, Kaposi sarcoma, and chest wall recurrence from breast cancer can be controlled [1,42–45]. Additionally, high response rates to early and late endobronchial disease are obtained as are complete response to Barrett’s mucosa and obstructing esophageal lesions [46–57]. Locally recurrent tumors of the rectum and anus can also be successfully treated [58,59]. Promising results have been seen in brain tumors [60–62] as well as head and neck neoplasms [63]. Bladder tumors are also responsive [64].

Clearly a wide variety of neoplasms as well as pre-malignant and even "benign" lesions can be treated on an outpatient basis with Photofrin®. The drug appears reliable, activatable, pain-free, and importantly, relatively safe and non-toxic. However, the drug is not highly selective at 2 mg/kg and significant prolonged photosensitivity is a real drawback. Without active intervention (i.e. limited sunlight exposure at controlled intervals) patients need to stay out of sunlight for at least 4 weeks. Room light is of no consequence. Accepted as part of Photofrin® PDT when 2 mg/kg is employed is significant normal tissue reaction from illumination. Just as the skin is very sensitive so too is illuminated normal tissue. While the drug does appear to concentrate in the tissue being treated as evidenced by a brisk response, the intercalated illuminated normal tissues also react, but less intensely. This can manifest as swelling of the skin for cutaneous lesions, but more frighteningly as necrotic tissue slough, particularly in airways. These extensive normal tissue reactions may be life threatening. Clinically, the use of steroids mediates the normal tissue reaction with no apparent oncological negative effect, but this should be studied further. This extensive normal tissue reaction is all too often accepted as a consequence of Photofrin® PDT. In reality, it is something that can be minimized by photobleaching. Photofrin® is a photosensitizer that can exploit photo bleaching and on this point alone offers great clinical flexibility. Photobleaching is an important concept and can be exploited clinically to partially make up for a lack of adequate dosimetry.

In the clinical arena, photobleaching is having just enough drug to react in tumors/tissue at risk, but no PDT in normal tissues. Currently no photosensitizer can accomplish this clinically. However, as Photofrin® generally accumulates a bit more in the tissue at risk, as compared to surrounding normal tissue, it may be possible to use an amount of Photofrin® per kilogram that accumulates in high enough concentration to give a clinically relevant amount of photodynamic reaction in malignant tissue, but does not accumulate enough in normal tissues to cause significant normal tissue damage. The drug appears reliable, activatable, pain-free, and importantly, relatively safe and non-toxic. However, the drug is not highly selective at 2 mg/kg and significant prolonged photosensitivity is a real drawback. Without active intervention (i.e. limited sunlight exposure at controlled intervals) patients need to stay out of sunlight for at least 4 weeks. Room light is of no consequence. Accepted as part of Photofrin® PDT when 2 mg/kg is employed is significant normal tissue reaction from illumination. Just as the skin is very sensitive so too is illuminated normal tissue. While the drug does appear to concentrate in the tissue being treated as evidenced by a brisk response, the intercalated illuminated normal tissues also react, but less intensely. This can manifest as swelling of the skin for cutaneous lesions, but more frighteningly as necrotic tissue slough, particularly in airways. These extensive normal tissue reactions may be life threatening. Clinically, the use of steroids mediates the normal tissue reaction with no apparent oncological negative effect, but this should be studied further. This extensive normal tissue reaction is all too often accepted as a consequence of Photofrin® PDT. In reality, it is something that can be minimized by photobleaching. Photofrin® is a photosensitizer that can exploit photo bleaching and on this point alone offers great clinical flexibility. Photobleaching is an important concept and can be exploited clinically to partially make up for a lack of adequate dosimetry.

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Energy or long treatments are needed. Despite using ALA is not highly active. So, relatively high light end-side chains used to increase absorption or activity. cannot be said for modified versions with altered ALA is a naturally occurring substance the same when deep lesions are treated[68]. Further, while penetrate to great depth, so caution is needed when topically administered, the drug does not slough noted after bronchial treatment of 2 mg/kg as well as the reports of fibrosis following therapy of Barrett’s esophagus. Clearly, photo bleaching by employing diminished drug dosage is an under appreciated way to enhance and exploit Photofrin®. Again, given the lack of adequate dosimetry one can conclude that Photofrin® is a relatively safe drug that appears very forgiving of what appears to be over treatment. This safety feature is what has allowed PDT to grow and be used in a wide variety of indications.

ALA

5-Aminolevulinic acid (ALA) is a prodrug[28]. This naturally occurring amino acid is converted enzymatically to protoporphyrin[66]. Fig. 2 shows the molecular structure for ALA. By topical administration one can create a clinical treatment course without light photosensitivity to untreated regions. Systemic administration does not have this built in selectivity[67]. The drug is active at 630 nm, which should give adequate depth penetration; however, when topically administered, the drug does not penetrate to great depth, so caution is needed when deep lesions are treated[68]. Further, while ALA is a naturally occurring substance the same cannot be said for modified versions with altered side chains used to increase absorption or activity. ALA is not highly active. So, relatively high light energy or long treatments are needed. Despite using topical anesthetics, ALA PDT can be painful. In general a preparation of 20% ALA is topically applied 4 h prior to illumination, which is done at 150 J/cm².

ALA-based PDT is highly successful against basal cell and squamous cell cancers of the skin[69,70]. Caution is to be observed as lesions approaching 1 cm will not usually be successfully treated by surface illumination. An ingenious and highly successful blue light system employing ALA for actinic keratosis with outpatient treatment as devised by DUSA Pharmaceuticals has FDA approval. Given the excellent cosmetic outcome, one might predict this system will become widespread in cosmetic and plastic surgery circles. ALA also has had success for head and neck tumors, though invasive lesions do not achieve complete response[71,72]. Given its limited penetration, ALA would more likely be at home for dysplastic and in situ lesions, which are rather common in the oral cavity. Topical 10% ALA, used in multiple sessions, successfully cleared more than 70% of patients with oral cavity leukoplakia with follow-up to 6 months[66,73–75]. Further, 17% ALA was intravenously infused in patients with recurring superficial bladder cancers[74]. Several hours after infusion, illumination was undertaken with white light at 100 J/cm². Treatment time was 1–2 h using a proprietary light catheter. About half the patients were rendered disease free. It is interesting to note that the white light activates multiple spectrum bands in ALA from 400 to 630 nm. This is a potentially underused type of illumination. 

PhotoCure ASA, a Norwegian company has employed methylated ALA (Metvix®) for a wide variety of lesions. The drug is topically applied and then about 3 h later red light illumination is employed. The drug/light therapy is approved in many European countries for treatment of actinic keratosis and basal cell lesions, with outstanding results[75–77]. However, pain remains a common morbidity during therapy. The same company produces Hexvix® for photodiagnosis and likely photodynamic therapy. Currently this drug is infused in the bladder and 30–60 min later blue light is employed to fluoresce abnormal tissue. This allows the urological surgeon an easy way to define lesions and surgically ablate them[78]. Ultimately, one hopes that PDT could be employed for ablation rather than just diagnosis[79], however, significant issues in dosimetry remain. Benzvix® is the drug Photocure ASA believes will allow for diagnosis and treatment of early esophageal and GI tract lesions.

ALA has been successful for esophageal treatment and with the oral form of drug this is convenient. Dysplastic epithelium can be reliably destroyed by ALA PDT[80–84]. Again caution must be advised for therapy of invasive lesions. ALA and its deriva-
100 J/cm² illumination is applied to leaky vessels in the eye. When 6 mg/kg Verteporfin i.v. is applied and hemorrhaging and destroying the choroids of the eye, destruction is a leading cause of blindness and so that skin photosensitization is minimal [86]. The drug is rapidly accumulated and cleared on neovasculature [87,88]. Age related muscular degeneration is a leading cause of blindness and its pathophysiology is based on vascular disruption and shutdown; therefore, response from Verteporfin sensitization is based on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; therefore, the drug would seem ideal for lesions depending on vascular disruption and shutdown; 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phototoxicity was reported. As a Phase 1 study, no clinical efficiency could be determined. However, the authors report a 4% decrease in arterial stenosis though follow-up was only 28 days. Similar promising results were seen in a Phase 1 drug and light dose escalation trial for coronary artery disease [103]. Antrin® was infused from 0.5 to 4 mg/kg with illumination of 200, 400, and 600 J/cm. Illumination at 732 nm occurred between 18 and 24 h postinfusion. A total of 80 patients were enrolled. The 12-min illumination itself was well tolerated, however, 12 patients experienced a periprocedural myocardial infarction. Again, dose related peripheral paresthesias and rash were commonly observed. Additional morbidity including chest pain and hypertension were seen. As this was a Phase 1 trial, no definitive therapeutic benefit could be assessed. No patient had sunlight photosensitivity and precautions were urged for 1 week postinfusion. Another promising venue would be therapy of neovascularity of the eye. Clinical results are pending.

Chlorin family

Temoporfin

Foscan® is a member of the chlorin family with a number of interesting clinical characteristics that have brought it to the forefront of newer photosensitizers [24,105,106]. Fig. 3 shows the molecular structure for Foscan®. However, many of the purported benefits of this photosensitizer are also potentially significant drawbacks. As a number of patients have been treated, some conclusions may be made, but only time and additional follow-up will allow for true assessment. However, it is clear that this drug offers excellent clinical control of a wide variety of cutaneous lesions [107–109], pulmonary [52,110–114], esophageal [51,115], GI [116–118], and especially head and neck tumors [71,119–124]. The drug is intravenously introduced and is associated with pain. The drug itself is dosed at 0.15 mg/kg. Clearly less drug is needed for successful PDT as compared to Photofrin®, but the cost of the drug used per patient is apparently equivalent. Illumination usually occurs 4 days postinjection, which can prevent emergent or unplanned therapy. The drug itself activates at 660 nm giving it somewhat greater depth of penetration. However, the optical properties of tumors in patients do not follow easily understood rules, so one can actually treat to much greater depths than predicted. In head and neck tumors, where m-THPC is commonly used, large blood vessels cover these regions and extra deep penetration leading to vascular damage could be catastrophic. The drug itself is highly efficient in converting light so that only 20 J/cm² is needed. This allows for fairly rapid treatment lasting, perhaps several minutes at the most. However, again significant pain can be experienced during treatment. Further, this photosensitizer is so efficient and treatment time so short that patient motion, from breathing, for example, can move the treatment field resulting in under dosage to tumor and/or over dosage to normal tissue. Further, as significant reflection can occur particularly in the mucosal regions, scattered light can be a problem. Extraordinary care must be taken to cover all regions that you do not wish to illuminate. Even with practice and equipment to devise light blocking devices, the potential for improper illumination is present. Interestingly, it usually takes far longer to block the scattered light than to treat. In many situations, for example, endobronchially, one cannot easily block light scatter. Given the highly efficient nature of this photosensitizer and the short time needed to create a PDT reaction it is unfortunately very easy to make a treatment mistake. With appropriate skill and appropriate blocking of normal tissues, excellent clinical and cosmetic outcomes have been obtained for cutaneous squamous cell and basal cell lesions, head and neck lesions, lung and esophagus all using 0.15 mg/kg and 20 J/cm². However, the treatment can lead to fistulas when used in the GI tract as well as circumferential fibrosis in the esophagus. Of note, modification of this photosensitizer by using 514 nm (Green) light for activation,
light doses of only 5 or 10 J/cm² with illumination easily. Despite using only 0.10 or 0.15 mg/kg and regions near the recurrence are very thin and damage appropriate for consideration is that the skin reagents and they are well versed in toxicity. Also radiation therapy, and multiple chemotherapeutic patients have undergone the rigors of surgery, radiation therapy, and multiple chemotherapeutic agents and they are well versed in toxicity. Also appropriate for consideration is that the skin regions near the recurrence are very thin and damage easily. Despite using only 0.10 or 0.15 mg/kg and light doses of only 5 or 10 J/cm² with illumination from 48 to 96 h after infusion, significant normal tissue toxicity was noted. This occurred despite using plaster as a means to protect uninvolved tissue. Even at these conservative treatment doses, normal tissue had substantial reaction with necrosis and slough. Treated areas larger than 12 cm² had the additional complication of delayed slough of large necrotic regions. It should be noted that these patients had undergone radiation therapy. One of these three had extreme pain and toxicity to PDT. This clearly could limit Foscan® use in this group of patients, as usually all patients with chest wall recurrence have failed radiation treatment prior to PDT. While illuminated tumors did not re-grow, new lesions appeared adjacent to treated areas [123]. This may well have been due to the extremely tight illumination margins needed to protect against excess normal tissue reaction. Again, it is important to emphasize that healing time, even with low drug and light dose, was measured in months. Notably, patients were photosensitive for at least 2 weeks and one patient suffered photosensitivity to the face due to exposure to a reading lamp.

Foscan® exemplifies how a photosensitizer that appears on paper to be ultra efficient and relatively rapidly metabolized with a high level of light penetration, still has clinical drawbacks. With current lack of dosimetry knowledge, this photosensitizer is very potent, but not always beneficially.

**Purpurin**

Purpurin (tin-ethyl-etippurpurin), a purpurin, is a degradation product of chlorophyll [126]. The drug is synthetic and pure, but due to poor stability in water must be formulated carefully. The current agent used as a carrier gives off an egg based allergic reaction. So, patients with egg allergies cannot be infused. The drug activates at 660 nm and so it should allow for good depth of therapy and is relatively efficient for short treatment times. In general 1.2 mg/kg is infused and therapy is offered at 24 h, which allows for easy scheduling. Clinical experience shows that the drug is effective in the treatment of basal cell, squamous cell, chest wall metastasis, and Kaposi sarcoma [127–130]. Cosmesis is excellent and pain during the therapy is minimal or non-existent.

**NPe6**

Among the chlorin family of photosensitizers NPe6 or mono-δ-aspartyl chlorin e6 has been brought to clinical trial [131,132]. In a Phase I trial [133] on cutaneous lesions, numerous clinically relevant data were found. With drug doses below 1.6 mg/kg all patients failed to achieve tumor control. With doses between 2.5 and 3.5 mg/kg the majority of lesions resolved. However, no tissue selectively occurred when 1.6 mg/kg or more drug was infused. This study also revealed that light doses of 100 J/cm² were favorable as was the therapy 4 h after infusion employing 664 nm of light. This lack of selectivity at clinically needed doses hampers the use of this drug in many clinical situations. However, a potential niche for NPe6 may exist in ophthalmic lesions [134]. While the drug appears safe it has the usual photosensitivity precautions.

**LS11**

Another chlorin-based photosensitizer, LS11, talaporfin Sodium is a water-soluble derivative with multiple absorption spectra including 400 and 664 nm [133,134]. The drug is excreted through the bile and precautions must be taken for patients with liver disease [135]. This drug is excreted fairly rapidly with a half-life of 9 h. What is particularly interesting is the outstanding miniature light device developed by Light Sciences to be used in conjunction with LS11 [136]. This palm sized source creates energy to illuminate a wide variety of LED's attached to a flexible fiber. In this case longer illumination is employed with the light source implanted interstitially in the patient through an outpatient.
Image Guided technique. This exploits a number of interesting photodynamic principles and may well change the way PDT is delivered. In a Phase I study the drug was introduced by slow i.v. push at 40 mg/m² (not kg). This was done after the light source was implanted via CT guidance. One-hour postinfusion treatment was given for various times ranging from 83 to 664 min, which corresponds to 250—2000 J/cm². CT scan was obtained posttreatment and regularly, thereafter, to assess response. Treatment was complicated by hypotension and cardiac changes in a few patients. Overall, toxicity was minimal and no photosensitivity was observed. Patients in the longer illumination groups achieved good response. A Phase II trial to further access this is underway. No clinical results are available for this drug with the more usual external light sources, but would be highly interesting to obtain.

HPPH

HPPH (Photochlor) is a chlorin-based photosensitizer with a number of excellent clinical properties [137]. This hydrophobic lipophilic photosensitizer is highly active at 665 nm and has successfully treated a number of naturally occurring tumors in dogs and cats [138,139]. The drug is intravenously introduced with minimal toxicity. The photosensitizer is effective at 0.15 mg/kg (6 mg/m²) and light dose at 48 h, of 150 J/cm at 665 nm. This resulted in eight out of eight patients achieving excellent response in esophageal cancers. Three patients with basal cell lesions were infused with 0.08 mg/kg (3 mg/m²) and illuminated at 24 h by 50 or 150 J/cm² versus 48 h at 200 J/cm². All schedules appeared effective. Several Barrett’s esophagus patients were clinical responses at 4—6 mg/m². Endobronchial recurrence from lung cancer may also be treated successfully at 4 mg/m². Patients appear to be sunlight photosensitive for several days after injection. This appears to be dependent on the dose of drug infused. While the number of patients infused remains small, clinically significant sunlight photosensitivity was minimal. With its excellent activity and relative safety, one may expect this to become a significant photosensitizer in the clinic [140].

Dye family

Dyes

Harking back to the days of Raab, dyes have been a fertile ground in which to develop photosensitizers. In fact, many of the dyes used in ink are efficacious photosensitizers. Most of the activity for clinical photosensitizers in the dye family, come from phthalocyanines and their relatives, the naphtho cyanines [141]. These structures are active in the 650—850 nm range and activate at energies around 100 J/cm². Most dyes are hydrophobic requiring delivery agents for clinical use such as a liposomal preparation. Linking dyes to a variety of metals seems to improve efficacy. Aluminum, zinc, and silicon appear to offer the best PDT activity. It is interesting to note that so far all the clinically successful dyes have structures similar to porphyrin [142].

Despite great interest in dyes, only a limited published clinical literature exists. Aluminum phthalocyanine tetrasulfate offered excellent clinical response in naturally occurring tumors in cats [143]. In addition, this dye and several others also allowed for fluorescence that could enhance treatment parameters [144]. Photosens, a sulfonated aluminum phthalocyanine, has had clinical success in a wide variety of cutaneous and endobronchial lesions. It has been used to treat malignancy and infection. Interestingly, the photosensitizer can be successfully formulated in several variations to allow for aerosol delivery, direct injection into lesions and intravenous delivery. In a report of 36 patients treated for malignancy and/or infection, excellent clinical results were reported [145]. Photosens has had success with head and neck tumors including the lip, pharynx, larynx, and tongue [146,147]. Tumors that failed initial therapy had a good chance for salvage with two PDT sessions. About 60% complete response was reported. Similar results were seen for cutaneous lesions of several histologies. Also of clinical interest is that these dyes also appear to have potential as radiosensitizers which could only increase their versatility [148].

Conclusion

The current family of photosensitizers on the market are—depending on your opinion—not selective or too selective, not efficient or too efficient, not pure or too pure, not able to penetrate deeply or able to penetrate too much, and the list goes on. Despite these drawbacks, successful PDT is possible not only on a variety of conditions, but under a variety of conditions. Once clinicians and scientists can speak the language of the photosensitizer, this drug will be able to screen for a medical condition through fluorescence, optically biopsy the lesion for diagnosis, treat the lesion by PDT, and tell us if we were successful or what more needs to be done by dosimetry.

It has been demonstrated that PDT has the potential to become a major weapon in our struggle
to treat and manage cancer patients. But this great hope is currently limited by the small number of (non-ideal) photosensitizers and unreliable dosimetry calculations. To overcome these difficulties, it is critical to rapidly expand our knowledge based on the fundamental mechanisms of PDT and the optical properties of various human tissues with and without photosensitizers. These challenges can only be met with an interdisciplinary research approach since PDT research is a field at the interface of physical, biological, and medical sciences. One example is the research team we have assembled at East Carolina University which includes optical physicists, medical physicists, computational physicists, imaging scientists, cell biologists, and physicians to move our research forward in multiple fronts of basic and clinical significance.

Ultimately, we will drink our magic sensitizing potion, sit through a total body photo-tomotherapy unit and have our ills washed away by light, just as Hippocrates advocated thousands of years ago, though in a little more complicated manner.

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