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Invited Review

Targeting Photochemical Scalpels or Lancets in the Photodynamic Therapy Field—The Photochemist's Role

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ABSTRACT

This review covers photochemical approaches aimed at supplementing surgical instruments with handheld photodynamic therapy (PDT) instruments. PDT is not widely used in hospitals, because of the laser equipment and expertise needed, and because insurance policies often do not cover the procedure. Accordingly, this review focuses on advances in photochemistry, photophysics, nanotechnology and miniaturization techniques that may likely inspire the use of handheld instruments in PDT. A takeaway point is that the advent of photochemical scalpels or lancets that deliver reactive oxygen species (ROS) on site may better equip medical practitioners and allow for eradication of tumors or infections in general. Specifically, the review is divided into several sections: sensitizer types, multiphoton and plasmonic topics, sensitizer delivery, light delivery, dosimetry, fiber optics and handheld implements in PDT.

INTRODUCTION

In this review, we focus on photochemistry and photodynamic therapy (PDT) in the context of surgical implements. Figure 1 shows surgical implements which vary based on tissue type, texture and shape, and level of manual control (1–6). Acknowledging the limitations of sharp surgical instruments, Kirkup has pointed to the advantages of cryosurgery, lasers and nuclear medicine (1–6). Gamma knife (7,8), cold plasma (9,10), robotic surgery (11) and PDT have also emerged as promising approaches in this regard (12–14).

For instance, cold plasma generated by jets or dielectric barrier discharges interact with biomolecules avoiding any thermal or electric damage to the cell surface and has been exploited in cutting, soft tissue coagulation and ablation (15,16). Several techniques are aimed at eradication of the cancerous tissues, which do not involve excision. This is the case of gamma knife, a stereotactic radiosurgery that has found application in the treatment of brain metastases (17,18), as well as of trigeminal neuralgia (see for instance: reference 19).

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Another approach is PDT, which works by generating reactive oxygen species (ROS) from nontoxic starting reagents sensitizer, $^3O_2$ and (visible) light, as shown in Fig. 2. Singlet oxygen ($^1O_2$, in the $^1\Delta_g$ state) (20–25), as well as superoxide radical anion ($O_2^{\bullet -}$), oxygen centered radicals (*e.g.* ROO$^\bullet$) and diradicals (26–37) are produced. The oxidizing nature of these species leads to cell killing (32,38–43), via different mechanisms including oxidative stress-induced apoptosis and necrosis (30,31). PDT often involves the intravenous administration of a sensitizer into the body, an incubation period that allows the sensitizer's localization at a lesion site, and the irradiation of the sensitizer-intercalated lesion.

In view of the above, a literature survey of photochemistry and PDT relative to the *cutting revolution* described by Kirkup (1–6) is presented. Such a connection has been largely neglected by prior reviews. Thus, the overview provided by this study invites the notion that photochemistry, photobiology and fiber optics are ripe for integration to design a PDT-type implement for use by medical professionals. The review consists of several sections: sensitizer types, multiphoton and plasmonics topics; sensitizer delivery; light delivery; dosimetry; fiber optics and handheld implements in PDT.

SENSITIZER TYPES, MULTIPHOTON AND PLASMONICS TOPICS

Sensitizer types

Due to their tunable photophysical properties, many of the sensitizers used in PDT have porphyrin, phthalocyanine or xanthene structures. The first to be clinically employed in PDT was porfimer sodium (also known as Photofrin® a mixture of hematoporphyrin derivatives) for lung, bladder and esophagus tumors. Figure 3 shows other sensitizers used including talaporfin sodium (**1**), chlorin e_6 (photolons), verteporfin (visudyne, **2**), purlytin, temoporfin and the pro-drug 5-aminolevulinic acid (ALA) (44–61). Other sensitizers such as motexafin lutetium (**3**), and bacteriochlorins padeliporfin and redaporfin are under investigation (48).

Research currently focuses on the desired properties of sensitizers, including easy and efficient syntheses, high extinction coefficients (ε = 20 000–200 000 M^{-1} cm^{-1} range), high

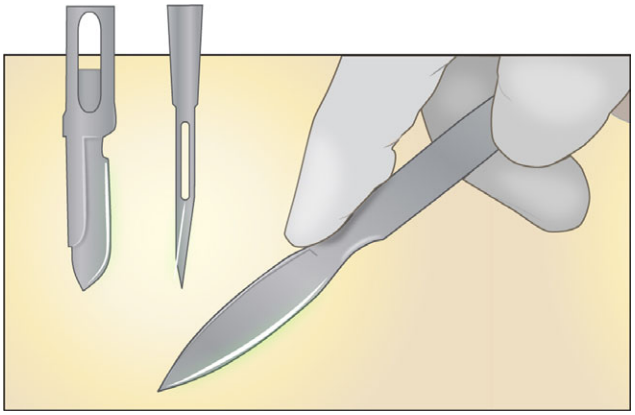


Figure 1. Shown graphically are handheld surgical instruments (left to right: curved scalpel, straight-edged scalpel, and lancet).

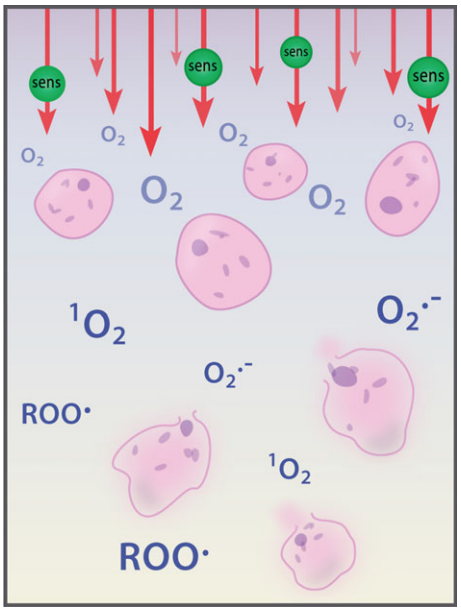


Figure 2. Schematic showing the combination of light, sensitizer and oxygen that results in the formation of reactive oxygen species (ROS) and subsequent cell killing.

singlet-to-triplet intersystem crossing efficiencies along with long triplet lifetimes, and resilience to photobleaching in order to preserve the sensitizer and protect its function as a catalyst (62,63). Additional properties that are sought are low levels of dark toxicity and good pharmacokinetics to clear the sensitizer and minimize the post-treatment side reactions. Some BODIPY derivatives (**4**) have met these criteria and have been successful in the photokilling of breast cancer cells (64). A common feature between sensitizers **1**-**4** is that they efficiently produce $^1O_2$. It is worth noting that multiphoton sensitizer absorption (discussed below) along with sensitizer delivery (discussed in the next section) are important considerations when designing sensitizers.

After a sensitizer is introduced by intravenous injection (for internal tumors) or topical application (for dermatology), it must localize at the target site (59). To this end, one strategy uses molecular recognition by cell markers such as receptor or antigen over-expressed on tumor surfaces. Tuning the substituent or conjugation with carbohydrates, amino acids, peptides or PEGs has led to improved localization in the target tissue (65–68). Because the folate surface receptor is over-expressed in several cell lines such as brain, nose, lung and colon cancer cells, folic acid has been successfully used as a sensitizer substituent for a targeted PDT (69–71). Sensitizers (approximately sized 20 Å) have also been conjugated to polymers (72), antibodies (sized 7–10 nm in diameter) (73) and aptamers (74) for improved delivery to tumors. For example, the target specificity PDT of chlorin e_6 was strongly improved by its conjugation to a 19 nucleotide RNA aptamer AIR-3A that binds efficiently the interleukin-6 receptor (74), allowing the internalization into the cell via receptor-mediated endocytosis. Failure to localize in organelles has been recognized due to sensitizers that are highly water soluble (75–77). Quantum dots (QDs) have been recently conjugated to sensitizers due to their increased photostability and because their optical properties can be shifted from the UV to the infrared region by tuning size, shape and composition, and their efficiency in acting as donor species in FRET processes (78–83).

In most cases, sensitizers are high in molecular weight and lipophilic, which can pose problems for their delivery (65,84–88), with a resulting loss of site selectivity and increase in toxicity. Indeed, even if adsorption by the target tissue occurs preferentially, some general distribution takes place, and if the sensitizer is not rapidly degraded in the skin, the result may be either irritation or the necessity to remain in the dark. The synthesis of more selective sensitizer or delivery vehicles would result in greater selectivity in the target tissue, and, consequently, less "free" sensitizer in the body. In the topical treatment of skin tumors, penetration and accumulation are mainly limited to the stratum corneum, with little sensitizer entering the tissue and therefore the tumor cells (89,90).

A key issue in PDT is light absorption by the sensitizer at the biological target (91). In dermatology, the sensitizer is applied topically where the light flux is easily measured and determining the efficacy of absorption is relatively simple. On the other hand, deep skin light absorption is limited to the red region of the spectrum (Fig. 4). Figure 5 shows a phototherapeutic window of approximately 650–850 nm, including limits imposed by water absorption above 900 nm (48). The sensitizer extinction coefficient mentioned above should be high (*e.g.* $\varepsilon > 20{,}000\ M^{-1}\ cm^{-1}$) in this phototherapeutic region of Fig. 5 (92).

Multiphoton topics

Sensitizers that absorb light in the phototherapeutic window in a multiphoton fashion have advantages for PDT. Multiphoton absorption causes the sensitizer excitation by two or more photons, where a single IR photon is not sufficiently energetic. The advantages to such an approach include (a) increased light penetration in tissue since sensitizers are often activated by red or near-infrared (NIR) light and (b) the potential to selectively excite the sensitizer in a complex mixture (93,94).

Progress in the field is focused on the design of compounds with high cross sections for two-photon excitation and by structural elaboration of known chromophores (95,96). As an example, porphyrins in general have a low two-photon absorption cross section, but a higher absorption cross section when they are made symmetric or when covalently bonded to electron donor substituents. Thus, a pyrrole-porphyrin conjugate (**5**) (Fig. 6) showed an excellent two-photon absorption that resulted

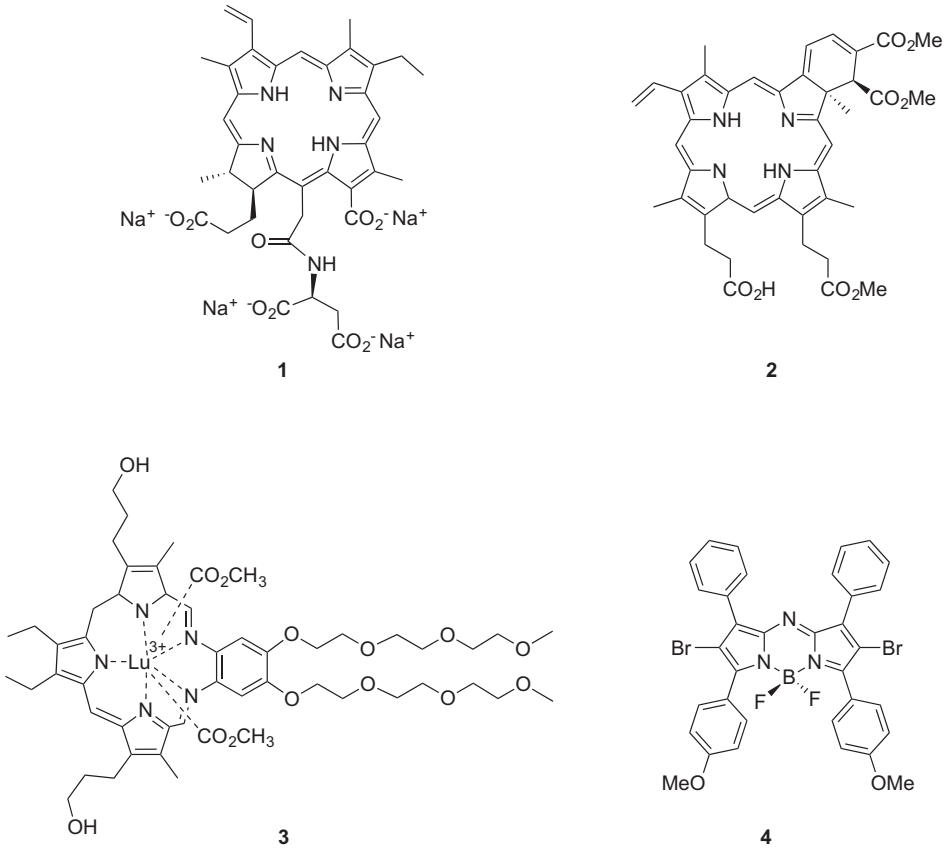


Figure 3. Examples of visible light or red light excitable sensitizers that are phototoxic: talaporfin sodium (**1**), verteporfin (visudyne, **2**), motexafin lutetium (**3**) and a BODIPY derivative (**4**).

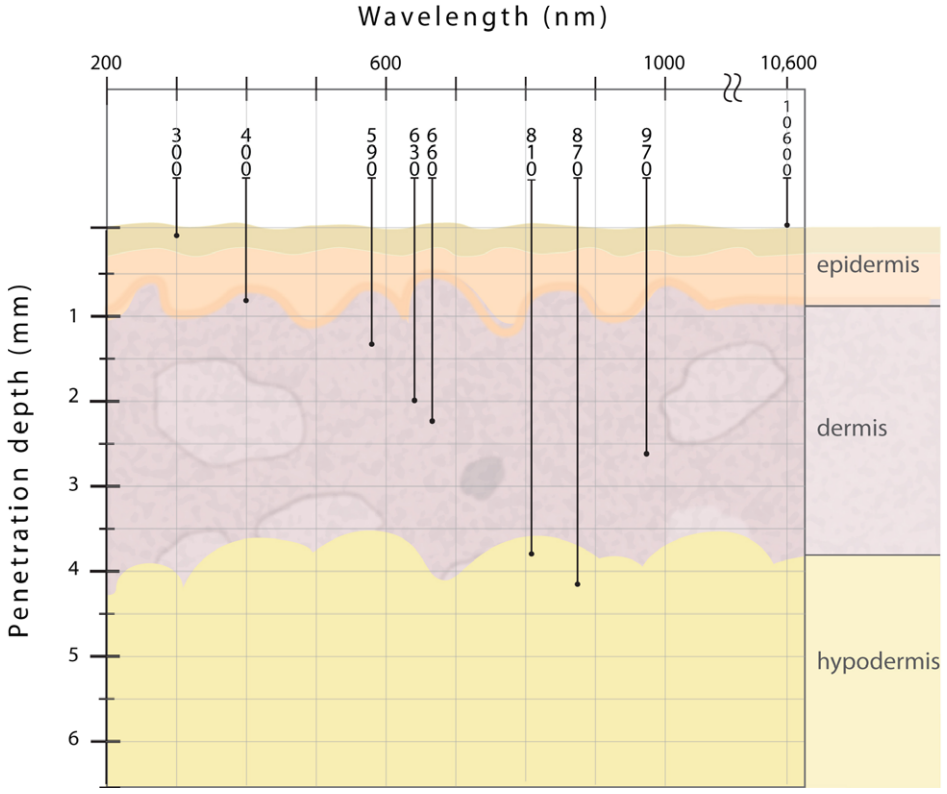


Figure 4. Schematic of the penetration of light of various wavelengths into skin.

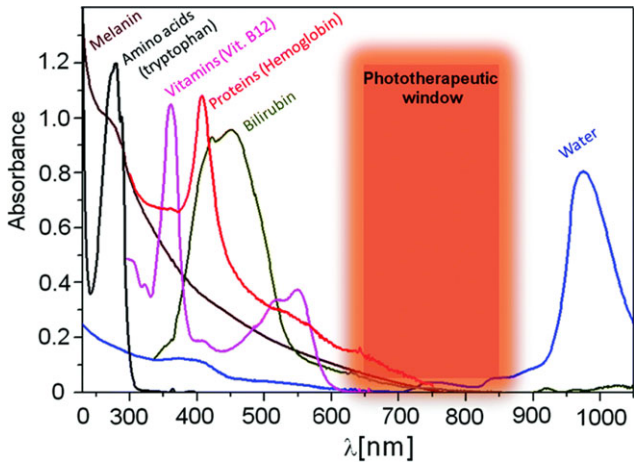
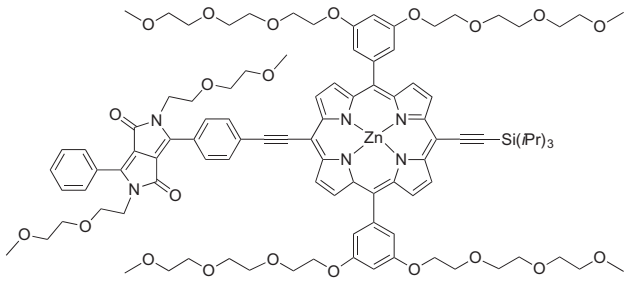


Figure 5. Absorption spectra of various biological materials showing an approximate location of the phototherapeutic window. The sensitizer extinction coefficient should be high in this phototherapeutic region. Reprinted with permission from reference 48.

in a high *in vitro* phototoxicity toward HEK cells (97). Alternatively, fluorescence resonance energy transfer (FRET) between a peripheral donor and the sensitizer core can be exploited for the development of NIR light ($\lambda_{ex} > 750$ nm) activable sensitizer. The absorption of NIR light ($\lambda_{ex} > 750$ nm) by the chromophore donors in porphyrin with a dendrimer-like structure (**6**), results in energy up-conversion and efficient transfer to the sensitizer core (98,99).

Microcapsules that are phototoxic upon either one- or two-photon excitation have been synthesized on the surface of a $MnCO_3$ microsphere by a layer-by-layer assembly of a polycation poly (allylamine) and a polyanion poly(sodium-para-styrenesulfonate). The layers were attached to a two-photon absorbing dye (fluorescein isothiocyanate) and also a one-photon absorption dye (rose bengal). The assembled system was characterized by a FRET between the sensitizers, the efficiency of which can be tuned by varying the assembly sequence and the chromophore. These microcapsules are a promising device in two-photon-activated photodynamic therapy for deep-tissue treatment (100,101).

Much recent attention has focused on two-photon absorption nanoparticle-based sensitizers. For example, Yb^{3+} and Er^{3+} co-doped Gd_2O_3 nanoparticles loaded with sensitizers such as methylene blue and pro-ALA can be efficiently taken up by human cervical cancer (HeLa) cells (102). When exposed to 980 nm laser light, these Gd_2O_3 nanoparticles emit red fluorescence, which activates the loaded sensitizers, thereby killing the HeLa cells via the formation of ROS (102). In the case of two-photon absorption systems, 720–930 nm femtosecond lasers are often used as the light source.



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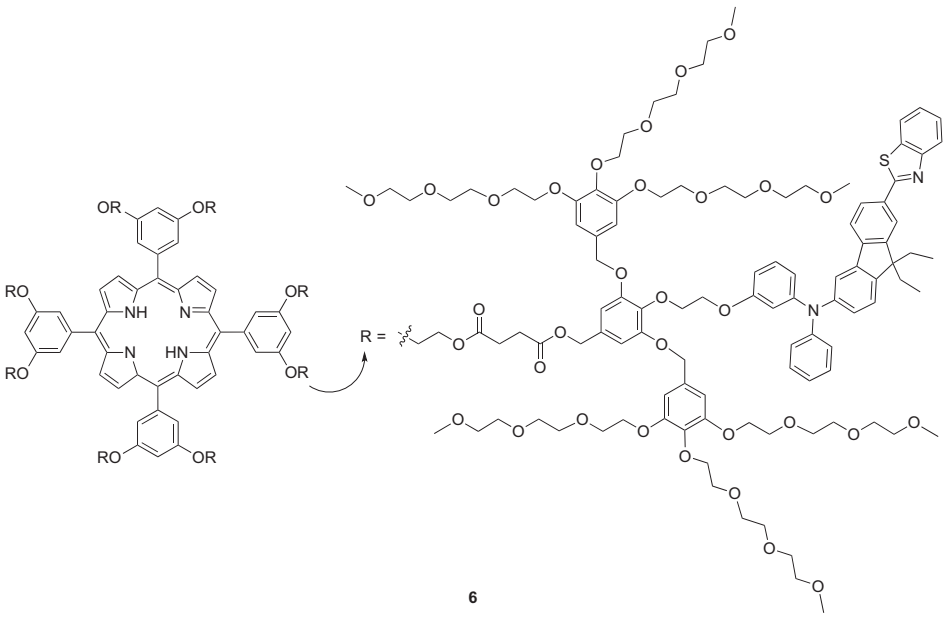

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Figure 6. Molecular structure of the two-photon sensitizer used in references 97 and 99.

Three-photon absorption may be even more advantageous than two-photon absorption, because its cubic dependence on incident-light intensity leads to superior spatial confinement of the excitation volume. Three-photon absorption also affords a much longer and penetrating excitation wavelength. In recent years, several molecular systems have been found to exhibit three-photon absorption, including hematoporphyrin IX (when pumping a DMSO solution of the sensitizer at 1200 nm) (103), trifluorenylamine (104) and carbazole derivatives (105), but only a few of them have been proposed for use in PDT. A three-photon absorption example is 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-alpha (HPPH)-doped colloidal mesoporous silica nanoparticles, which showed an *in vitro* phototoxicity toward HeLa cells when irradiated under 1560 nm light pulse (106). Lastly, four photon-excited fluorescence resonance energy transfer was reported between ZnSe:Mn/ZnS quantum dots and hypocrellin A and was successfully used in the photokilling of breast cancer cells (MCF-7), with a death cell rate of up 85% with 1 mM concentration of hypocrellin A (107).

Plasmonics

The use of plasmonic systems in PDT is a relatively new field of study. Sensitizers bound to metal particles or silica have been found to increase singlet oxygen production, electric field or enhanced sensitizer absorption, and/or singlet oxygen luminescence efficiency (108–117). There have been reports of plasmonic systems with increased PDT efficiency (118–121). One was described by Gao *et al.* (122), who reported that NIR irradiation gold nanocages with low power intensity (0.40 pJ per pulse) resulted in the initial generation (from the surface plasmons excited) of hot electrons that were responsible for the sensitization of oxygen to ROS through either energy or electron transfer modes and the consequent apoptosis of HeLa cells (Fig. 7). It has also been found that plasmonic gold nanoparticles loaded with chlorin e_6 led to the photokilling of human breast cancer cells (123). Plasmonic copper sulfide nanocrystals ($Cu_{2-x}S$, calculated to be $Cu_{1.9}S$) have also been used in the generation of ROS for the non-invasive sterilization of mice (124).

SENSITIZER DELIVERY

The previous section of this review describes various sensitizer types, multiphoton absorption and plasmonic systems that have been used for the production of ROS and in PDT. Advances have also been made in sensitizer delivery systems.

Chemical approaches with the development of various vehicles

Vehicles such as liposomes have also been reported as effective ways in the delivery of drugs and sensitizers (125–132).

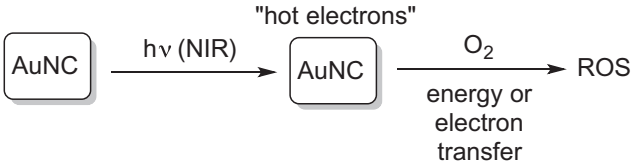

Figure 7. Generation of ROS via NIR irradiation of gold nanocages.

Liposomes are spherical in shape and their size varies from 15 nm to 1 μm in diameter, where most are 50–300 nm in diameter. Sensitizer and drug encapsulated liposomes are also commonly used for delivery to target sites with localization and distribution. Sensitizers have been bonded to nanoparticles (133,134), which possess large surface areas and have diameters of 1–100 nm; medium-sized particles have diameters of 100 nm–2.5 μm, whereas large particles have diameters of 2.5–10 μm. Sensitizers are often sized ~20 $Å^2$ and fit into inorganic materials, such as zeolites (cage diameter of ~0.7–1.0 nm), aluminum phosphate (channel diameter of ~0.7–1.0 nm), silicas such as MCM-41, MCM-50 and SBA-15 (channel diameters of several nanometers), and clays such as smectite and montmorillonite (with layers varying in width) (135). Microneedles and microsyringes have also been reported as effective ways to deliver sensitizers.

Instruments and engineering

In order to overcome the problems related with the penetration of sensitizer into tissue, microneedles have been used to create micron-sized portals (136). The tip diameters of ~5–150 μm and short length of the microneedles do not lead to nerve penetration in the dermis layer and thus are usually painless, which is in contrast to hypodermic needles (*e.g.* ~500 μm diameters) (137). Drug delivery into the skin can take place by several mechanisms. In the simplest case, solid microneedles are used to pretreat skin; then, the drug diffuses through holes from a topical formulation or from a patch. Alternatively, drug-coated and drug-loaded microneedles are penetrated into the skin, allowing for the diffusion of the drug in the dermis through solubilization of the coating and dissolution of the biodegradable microneedle, respectively. Finally, a liquid formulation can be directly injected into the skin by means of hollow microneedles (138).

Microneedles have been used for transdermal delivery of a variety of drugs and therapeutic agents including vaccines (139), insulin (140) and nanoparticles (141) with permeation of these agents in a perpendicular direction relative to the surface of the skin (142–144). Microneedles have been used in the topical delivery of both preformed sensitizers and pro-sensitizers for photodynamic therapy (145). For example, treatment of excised porcine skin with silicon microneedles arrays and later with a bioadhesive patch charged with *meso*-tetra(*N*-methyl-4-pyridyl) porphine cation was found to improve *in vitro* intradermal delivery of the sensitizer. The same approach was successfully tested *in vivo* (146). Studies of pro-sensitizers were carried out using hydrophobic dyes as model compounds; thus, the delivery of nile red dye-encapsulated poly-lactide-co-glycolic acid nanoparticles through tissue indentations from microneedle arrays was also demonstrated (Fig. 8) (147). The use of microneedle patches containing 57 microneedles coated with pro-sensitizer 5-aminolevulinic acid (ALA, 350 μg per patch) resulted in a ~90% delivery efficiency *in vitro* (porcine cadaver skin), and dermal pharmacokinetics *in vivo* showed that sensitizer protoporphyrin IX formation takes place in 3.2-fold higher concentration, and it is observed in deeper regions of the skin (~150 μm × ~480 μm) ($d \times l$) as compared to topical application of 20% w/w 5-ALA in a conventional cream formulation. The microneedles make a hole 150 $μm^2$ into the tissue. For this reason, microneedle patches were suggested to be more efficient for treating subcutaneous skin tumors than topical cream (148). Microneedles,

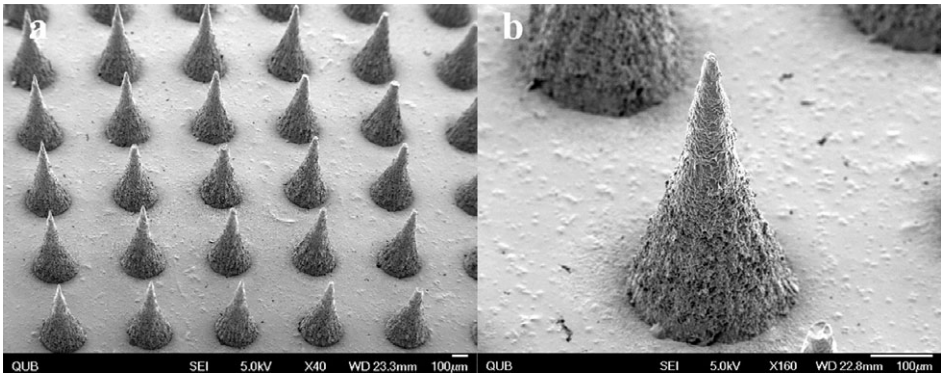

Figure 8. SEM images of a microneedle patch (a) and an individual microneedle (b). Reprinted with permission from reference 147. Copyright 2010 Elsevier.

however, have seen limited use in the delivery of sensitizers for PDT.

The development of microsyringe systems has occurred (149–152), which can offer a means to deliver sensitizer. A microsyringe attached to an endoscope was successfully fabricated and exploited for injection of a drug dissolved in a carrier solvent (152). Microsyringes were applied to the delivery of the drug tacrolimus and dye-conjugated taxol into artery tissue in swine (151) as reported by Fumiaki *et al.* Fig. 9 shows an example of a commercially available microinjector with short plungers ~50 mm and tube lengths of 1 m to deliver drug solution volumes of tens of nanoliters up to microliters. Capillary sizes are typically 0.5 μm i.d. and 1 μm o.d. Furthermore, the flow can be controlled. It is worth noting that catheters have long been used for drug delivery and are often plastic or rubber tubes with o.d. values from tenths to double-digit millimeters. Reports about microsyringes are mainly related to analytical applications (153,154), including the transfer of a drug from aqueous medium to a lipophilic medium (155). Based on these applications, one can conjecture their use for the delivery of sensitizers. Up until now, however, microinjectors that can deliver sensitizer by endoscopy have not been a major focus in PDT.

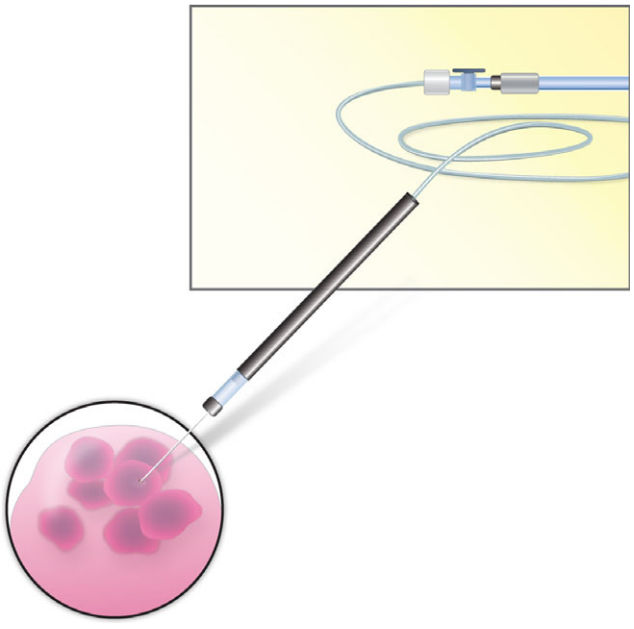

Figure 9. A graphical image of a microsyringe.

LIGHT DELIVERY

Once the sensitizer has been localized to a specific site, irradiation of the site is needed. This section presents examples where light itself provides for spatiotemporal control of sensitizer activation where PDT is needed. Researchers have been active in developing light delivery systems with uniform illumination, which is essential for reproducibility. Thus, bulb-shaped isotropic emitters along with light detectors have been used in hollow organs, for example, in the treatment of superficial bladder cancer. In this way, light dosimetry helps to optimize the positioning of light diffuser (156). Furthermore, elaborated diffusers such as balloons and cylindrical applicators are used, with the form and dimension suited to the case, thus catering to the selectivity of PDT. For example, Fig. 10 shows an indwelling balloon applicator for the PDT treatment of glioma, which has been investigated *in vitro* by Madsen and co-workers (157,158). This device works in a way such that the insert sits on the cranial bony surface and no forces are transmitted into the brain. In addition, as the entire apparatus is covered by intact skin and the central lumen is sealed at both ends, there is no contact with the brain or other biological tissue or fluids, and therefore, and the risk of infection is minimized (159). Here, intralipid fluid, a lipid emulsion, was circulated through the cavity after tumor resection to help scatter the light (160).

Table 1 summarizes light sources that are commonly used in sensitizer excitation. In dermatology, LED and diode lasers have replaced expensive and difficult-to-handle Argon and Argon-pumped dye lasers. They are commonly used due to their robustness, short bandwidth, relatively low maintenance cost and ability to be configured to the wavelength required by the sensitizer. Other lamps such as Tungsten filament lamps, metal halide lamps and powerful Xenon arc lamps have been also used (160,161). A dual wavelength emission (630 and 405 nm) LED device has been employed for the PDT of skin and hair follicles; the longer wavelength is used to reach the desired target (the sebaceous glands), while the blue emission is employed to photobleach and thereby remove residual amounts of sensitizer, minimizing post-treatment photosensitivity (162). Pulsed lasers are also commonly used in the PDT field (163–167).

Where endoscopic applications are needed (168–180), optical fibers are used, as in the case of the PDT of esophageal cancer

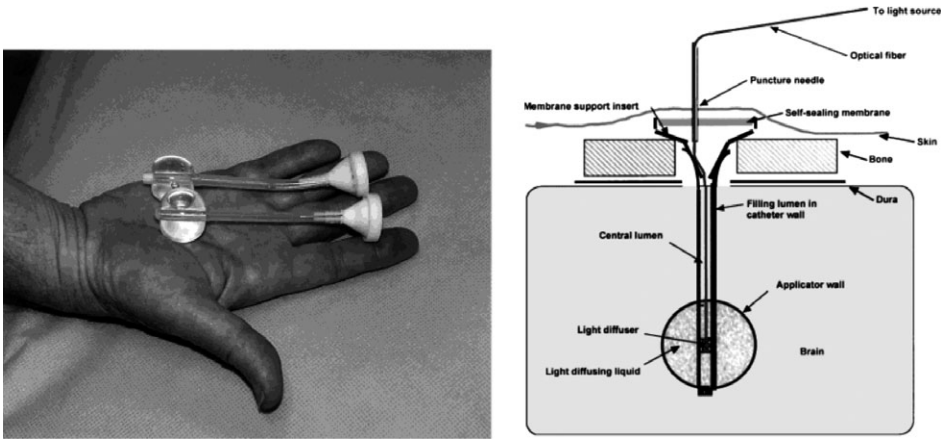

Figure 10. Picture of the indwelling balloon applicator and schematic application of the device in photodynamic therapy of glioma. Reprinted with permission from reference 157.

Table 1. Common light sources used for sensitizer excitation (Adapted from reference 160).

Light source	Wavelength range (nm)	Pulse duration, irradiance (mW cm^{-2})
Argon-pumped dye laser	500–750 (depending on the dye)	CW, 10–200
Semiconductor diode laser	600–950	CW, up to 700
Tungsten filament	400–1100	CW, up to 250
Metal halide	250–730	CW, up to 250
Xenon arc	300–1200	CW, up to 300
Light emitting diodes (LED)	Visible, infrared region	CW, up to 150

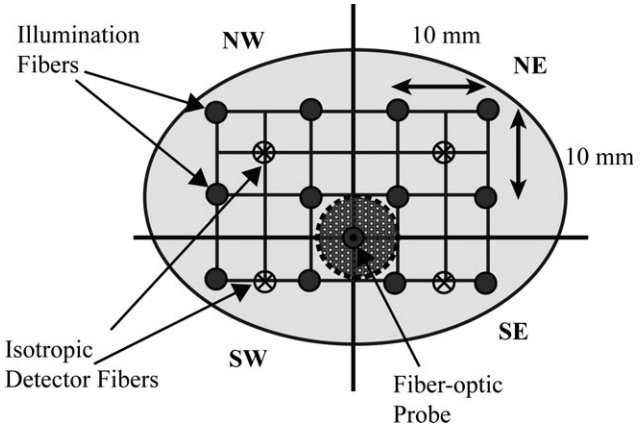

Figure 11. Cross-sectional view of the fiber positions for all quadrants in the treated prostate. Redrawn with permission from reference 203.

(181–183). Specifically, flexible diffusers based on plastic optical fibers are well suited for curved surfaces and cavities. For example, a 1×4 fiber splitter that delivers PDT simultaneously through four flexible cylindrical optical diffusers has been used for prostate PDT (184). In another instance, prostate cancer PDT was carried out by intravenous infusion of padeliporfin (TOOKAD®) sensitizer, while the targeted area was illuminated by transperineal optical fibers inserted under trans-rectal ultrasound guidance under general anesthesia (161). PDT has also been applied to canine models for cardiac catheter ablation. In this case, talaporfin sensitizer was used with a flexible laser catheter as the light source (185,186). The PDT approach is an improvement from traditional methods, such as radiofrequency ablation, which cause heat induced lesions.

As implied in this section, there are issues associated with the delivery of light to the sensitizer. It is yet unclear what light source would be practical for a PDT-type scalpel or lancet. Advances in the development of handheld biomedical devices will be discussed in a subsequent section.

DOSIMETRY

Increasing the effectiveness of PDT involves optimizing parameters, such as sensitizer concentration, oxygen concentration, light dosage and singlet oxygen production (93). Dosimetery helps to ensure the targeted area receives PDT while preventing damage to normal tissue (187,188). Both explicit methods (for measuring of sensitizer and oxygen concentrations and singlet oxygen and light dose delivered) and implicit methods (using parameters such as sensitizer photobleaching as indicator of the effective treatment dose administered) have been proposed (92,187–196).

The measure of singlet oxygen concentration has been a challenge (197), but is one of the most important parameters to optimize. For example, a compact fiber-optic-based singlet oxygen near-infrared luminescence probe was coupled to an InGaAs/InP single-photon avalanche diode (SPAD) detector as a highly sensitive method (198). Patterned time gating of the single-photon detector was exploited to exclude both undesired dark counts and the strong sensitizer luminescence background. The effect of light scattering to the sensitizer was also examined as a first step toward applications in tissue *in vivo* (198). Another way to measure the level of singlet oxygen production was described by Hála *et al.* and involves a setup in which parallel temporal and spectral resolutions were used for simultaneous measurement of sensitizer and singlet oxygen phosphorescence (199). In the apparatus, a pulsed excimer laser (420 nm) acted used as pump, while the luminescence generated by the photoexcited species was collected by lens assembly through a long-pass filter and high luminosity monochromator and detected by an infrared sensitive photomultiplier. Using this approach, singlet oxygen was efficiently monitored *in vitro* layers of cultured T3 murine fibro

blasts and HeLa cells (199,200). The detection of the weak singlet oxygen emission produced in both *in vitro* and *in vivo* experiments has also been measured by means of a fiber-optic-coupled, pulsed diode laser-based diagnostic devices. The obtained signal was filtered both specially and temporally to isolate the singlet oxygen from long wavelength sensitizer emission (200,201).

A multicanal device combining diffuse reflectance spectroscopy and diffuse correlation spectroscopy for the measurement of tumor blood oxygenation and blood flow respectively was adapted for the measurement of different parameters during interstitial prostate motexafin lutetium-mediated PDT (202,203). Photophysical parameters for human prostate cancer include distribution of light fluence rate, oxygen saturation, total blood volume, and sensitizer concentration. These parameters have been efficiently determined by means of different sensing techniques and devices, such as interstitial isotropic detectors, fluorescence, and diffuse absorption spectroscopy (202,203). A similar approach has been used in the PDT of prostate tumors (Fig. 11) (204) and skin tumors (205,206). The light treatment (732 nm) was administered by means of cylindrical diffusing fibers inside the catheters (solid circles), whereas the distribution of light during the PDT was monitored by an isotropic-detector fiber (cross-circles) placed in the center of source fibers. A fiber-optic probe

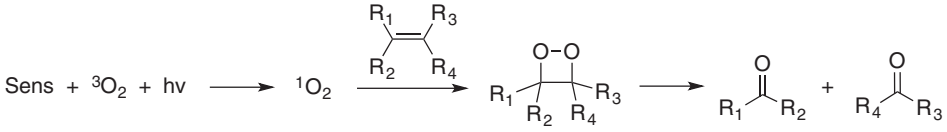

Figure 12. Photocleavage of an alkene bond via the scission of a dioxetane intermediate.

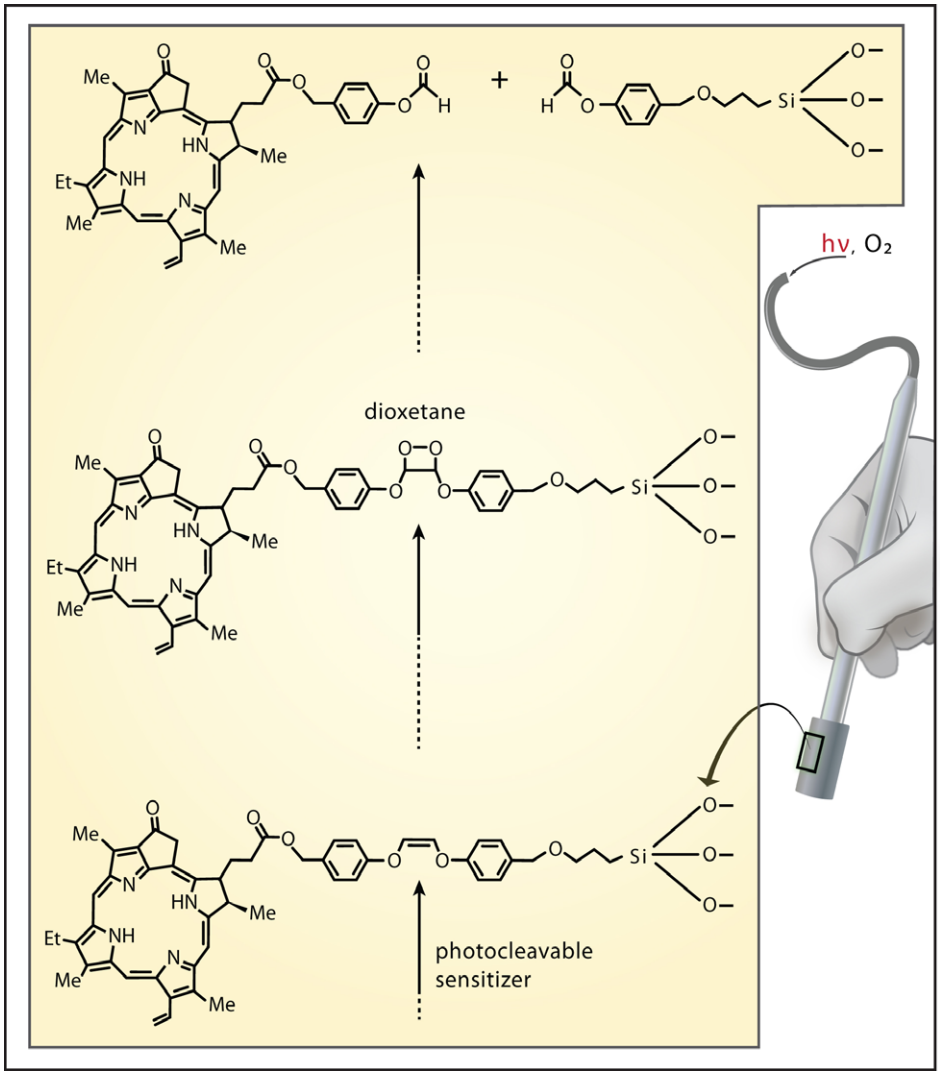

Figure 13. A fiber-optic tip (5 × 8 mm^2) made of porous silica that photocleaves sensitizer molecules by the decomposition of a dioxetane intermediate. The fiber optic has a gas flow tube that is connected to an oxygen gas tank.

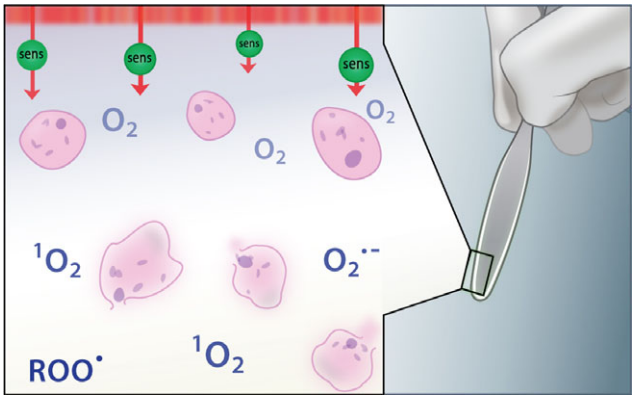

Figure 14. Schematic of a handheld photodynamic therapy probe that delivers reactive oxygen species to specific sites for use by healthcare professionals.

consisting of one source and five detector fibers was placed before treatment through the catheter in the center of the quadrants (double circle) and stayed in place throughout PDT to tumor blood oxygenation and tumor blood flow, respectively. During the treatment, the four quadrants of the prostate were illuminated sequentially. Such a multicanal approach allowed for the simultaneous identification and the real-time measurement of the essential parameters. The quantification of the above mentioned parameters is important in optimization of PDT effectiveness (188,206).

FIBER OPTICS AND HANDHELD IMPLEMENTS IN PDT

Thus far, our review has addressed sensitizer types and how light is delivered to the sensitizer. The previous section described dosimetry methods including the use of fiber optics and the measurement of sensitizer concentrations, oxygen concentrations and reacted singlet oxygen. The use of such a broad scope in this review is to suggest that an integration of PDT and nanotechnology could lead to the development of a photochemical scalpel or lancet.

Several studies have shown that fiber optics can be used in photorelease processes. One report discussed a fiber-optic system (207) that used cultured neurons and brain slices with caged reagents that underwent photo-*un*caging reactions where the laser spot was focused. Other papers have reported on functionalized alkenes reacted with singlet oxygen, leading to a [2 + 2] cycloaddition and then cleavage of the alkene moiety via a dioxetane intermediate (Fig. 12). Reports have described visible or NIR light to disconnect drugs from sensitizer molecules, as a means for simultaneous PDT and delivery of anti-cancer drugs, such as paclitaxel (208–211). Related NIR uncaging and sensitization reactions have also been reported for cyanines and phthalocyanines (212–214). Papers have also reported on a pointsource device that sparged oxygen gas and photochemically released sensitizer molecules for ROS to kill glioma cells and ovarian cancer cells (Fig. 13) (215–217). The pointsource device used a red diode laser with an optical fiber connected to a silica tip. The borosilicate fiber optic was 3 ft in length, had an inner gas flow tube (0.23 mm i.d., 0.46 mm o.d.) running from the distal end to a T-valve surrounded by ~60 excitation fibers in a ring around it, and was encased in a polyvinyl chloride jacket (1.09 mm i.d., 1.50 mm o.d.) which delivered 0.5 mW out of the end of the fiber. Much of the red laser light was distributed out the end of the tip rather than scattered evenly within the tip. The silica tip has a small cylindrical shape. Research to improve the fiber-optic system was carried out with the intention of creating a PDT device that works as a pointsource anticancer treatment. A "nonsticky" tip was also designed for resistance to fouling in the presence of biomaterial such as proteins, cells or microorganisms, in which further cancer cell eradication studies will likely prove useful (218). Related fiber-optic technology has been reported with oxygen sensing reactions (219–223).

PROSPECTIVES AND CONCLUSION

This review covers advances in photochemistry and highlights how implement design and development may facilitate further success in the field of PDT. However, as the assembly of handheld PDT instruments is required, such instruments cannot simply be purchased commercially. The prototype instrument shown in Fig. 13 may be the first step toward a new class of PDT instruments as shown in Fig. 14. If such instruments were developed by combining techniques ranging from photochemistry and materials synthesis to engineering, use of PDT may be facilitated in a surgical setting.

In this review, we present specific areas where we may be able to implement basic and applied techniques to develop handheld PDT instruments that make an impact in the surgical field. In this vein, further research on microneedle, microinjector and fiber-optic tips could provide new avenues for delivering sensitizers, as well as oxygen and light on site. Much additional effort is still needed, and it is still uncertain whether PDT-type scalpels or lancets will one day fill a niche alongside surgical implements. However, the development of such handheld PDT instruments is plausible, and we look *forward* to future studies in this field.

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