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Editorial: Photodynamic Therapy and Detection

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This special issue on photodynamic therapy (PDT) and detection has been assembled by the guest editor by soliciting individual contributions from specialists in the field throughout the world. Photodynamic therapy is a combination of light with photosensitizing agents and oxygen present in a tumor, leading to photochemical and photobiological reactions that result in irreversible photodamage to the tumor.[1] During this process a photosensitizer absorbs energy from light. The absorbed energy can be transferred to molecular oxygen to produce singlet oxygen ($^1O_2$) and oxygen radicals, which are highly toxic and react further with cellular components to cause cell death. The absorbed energy can also be passed off by fluorescence, which can be utilized for tumor photodetection (PD).[1]

Although the light was used for the treatment of vitiligo 3000 years ago by the Indians, the Egyptians, and the Chinese,[2] the real era of PDT began with the discovery just over one hundred years ago by Oscar Raab, a medical student working in the group of Hermann von Tappeiner in Munich, who accidentally found that illumination of a thunderstorm could kill paramecia in the presence of acridine.[3] This finding was followed in the same group by clinical PDT treatment of some skin non-malignant and malignant diseases with topical and intratumoral administration of photosensitizing compounds.[4] The current era of PDT and PD probably began with studies by Lipson and Schwartz at the Mayo Clinic in the 1960s, who found fluorescence in tumor tissues following injection of crude hematoporphyrin (HP). Modifications of the HP led to the development of hematoporphyrin derivative (HpD, a porphyrin mixture), which was a better tumor localizer than the crude HP.[5-7] The properties of HpD as a tumor localizer and phototherapeutic agent were systematically studied by the Dougherty's group in the 1970s and 1980s at the Roswell Park Cancer Institute in Buffalo, New York.[8,9] The purified version of HpD with monomers removed was made by the same group and named Photofrin, which was approved for clinical use by regulatory health agencies worldwide.[8-10] Thanks to the pioneering work of this group. Photofrin is probably the most widely used sensitizer in the clinic. However, Photofrin is a complex mixture of porphyrins with widely differing properties and weak light absorption at wavelengths above 600 nm where light penetration into tissue is optimal. Moreover, the clinical application of Photofrin is limited by prolonged cutaneous photosensitivity resulting from its slow plasma clearance. These shortcomings stimulated the search for pure compounds with rapid plasma and tissue elimination, enhanced tumor selectivity and strong light

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absorption of optimal wavelengths. A number of second-generation photosensitizers have been introduced: phthalocyanines, chlorins, purpurins, and benzoporphyrins. Some of them are being investigated in clinical trials, such as meso-tetra (hydroxyphenyl)chlorin (mTHPC), Chlorin e6, benzoporphyrin derivative monoacid ring A (BPD-MA), tin ethyletiopurpurin (SnET2), lutetium texaphyrin (Lu-tex),[1] and porphyrin precursors, 5-aminolevulinic acid (ALA) and its derivatives.[11,12] Current clinical PDT studies include tumors of the skin, gastrointestinal tract, head and neck, lung, brain, bladder, pancreas, female reproductive tract, prostate, and intraperitoneum, as well as non-malignant proliferative tissues of choroidal neovasculature (the wet form of age-related macular degeneration, AMD), actinic keratosis, and acne.[1,10,13] Among the second-generation sensitizers BPD-MA (Visudyne) for AMD, ALA (Levulan) for actinic keratosis, ALA methylester (Metvix) for actinic keratosis and skin basal cell carcinoma, and mTHPC (Foscan) for head and neck cancer have been approved by regulatory health agencies in many countries.[10] It should be pointed out that the involvement of several pharmaceutical companies has largely sped up the development of PDT and PD techniques.

Light is one of the three parameters determining PDT efficacy. Today, the standard light source for clinical PDT is lasers, since the laser beam can be efficiently coupled into single optical fibers, which are further inserted in flexible endoscope systems used for internal hollow organs. The laser most frequently used is the argon dye laser. Diode lasers have now become commercially available and are probably the best choice (convenient size and easy to use) for light sources, if only one sensitizer is to be used. Filtered lamps and light-emitting diodes (LEDs) may also be applied for surface irradiation. Light fluences are applied in a wide range of 10–-500 J/cm^2, depending on the sensitizers with various extinction coefficients in the wavelengths used. Normally, the surface irradiance of lower than 200 mW/cm^2 does not generate a hyperthermal effect during PDT. Interstitial irradiation with diffusing fibers inserted into a tumor can also be used.

The amount of oxygen present in tumor is a crucial factor for PDT effectiveness.[14,15] The oxygen concentration can be depleted during PDT as a result of either photochemical consumption or vascular damage. Light dosimetry can significantly affect tissue oxygenation. There is a great need for the development of techniques allowing real-time monitoring of oxygen levels in tumor tissues.

Photodetection is based on fluorescence spectroscopic, endoscopic and imaging techniques to demarcate lesions from surrounding healthy tissues.[16] The specific fluorescence in tissues is induced by a laser with a suitable wavelength, in most cases with prior administration of a sensitizer or its precursor. These techniques are being evaluated to detect malignant diseases in the fields of urology, gynecology, and gastroenterology. They can also be performed together with conventional white-light endoscopic examinations to increase the diagnostic accuracy.[17] Very recently, Hexvix, a product of PhotoCure ASA, Oslo, has been approved by the European Union (EU) for clinical photodetection of bladder cancer. Since sensitizers used for PD and PDT are usually the same compounds, an ideal system should be constructed with starting PD of a lesion followed by PDT of the lesion within a single setting.

As yet, no universal mechanism by which PDT works has been described; it may have different mechanisms depending on the type of the tumor treated, the type of photosensitizer used

and the light dose/interval protocols. Since $^1O_2$ in cells has a lifetime of less than 0.05 μs with a maximal diffusion of 0.02 μm from the site of its production,[18] the subcellular and intratumoral targets of PDT are the places where the sensitizer is localized.[19] Photosensitizers are often taken up by tumors with some selectivity. This selectivity is probably not due to special properties of tumor cells,[20] but rather to the differences in the physiology of tumors and surrounding normal tissues.[21] It may also be related to the chemical properties of sensitizers. Generally, hydrophilic sensitizers localize mainly in lysosomes of cells and stroma of tumors, whereas lipophilic dyes distribute largely in membraneous structures of cells (e.g., plasma membrane, mitochondria) and cellular components of tumors.[22,23] Illumination of tumor-localizing sensitizers leads to cell necrosis[1] and apoptosis.[24] In addition, PDT-induced vascular and immune responses play crucial roles in tumor destruction and perhaps also prevention of tumor recurrence. Increased understanding of these mechanisms has led to improved PDT efficacy by using angiogenic inhibitors[25,26] and immunotherapy agents.[27,28] Photochemical internalization (PCI), a new technique for delivery of endosome-trapped macromolecules into the cytosol, is also based on the PDT principle.[29]

New nonmalignant indications are being evaluated for PDT and PD. They include peripheral vascular restenosis secondary to balloon angioplasty and atherosclerosis, psoriasis, rheumatoid arthritis, acne, menorrhagia, and benign prostatic hyperplasia. In addition, bone marrow purging and PDT of certain bacterial, fungal, and viral infections are being studied.[30]

So far, three photosensitizers and three porphyrin precursors have officially been approved by FDA or EU for PDT and PD of malignant and nonmalignant conditions, but the techniques are still faced with the great challenge of general clinical acceptance. Nevertheless, the modern era with studies on cell death mechanisms, combined modalities, immunological response, etc.; and with applications for both malignant and nonmalignant conditions deviates largely from the initial intents of Oscar Raab and Hermann von Tappeiner. The techniques of PDT and PD with diverse potentials make one believe that visible light rays with the help of light-activated drugs can contribute to our armamentarium.

It is a great honor for me to act as a guest editor for this Special Issue. Many thanks to all contributors for their excellent contributions. I want also to thank Dr. William Begell, President, and Vicky Lipowski, Production Manager, of Begell House, Inc., for their support and cooperation.

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