Published in final edited form as:

Cancer Res. 2016 May 01; 76(9): 2497–2499. doi:10.1158/0008-5472.CAN-16-0927.

PDT: What's Past is Prologue*

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Abstract

Despite descriptions of light-mediated therapy in ancient texts and the discovery of photodynamic therapy (PDT) in the early 1900's, the landmark paper in 1978 in *Cancer Research* by Dougherty and his colleagues at the Roswell Park Cancer Institute remains rightly viewed as the starting point for clinical PDT in modern medicine. As a large clinical series that explored many of the factors now viewed as critical determinates of PDT dose, efficacy and toxicity, that study showed remarkable foresight, yet it also served to raise as many questions as it answered. Since its publication, PDT has become increasingly utilized in clinical practice for the treatment of both benign and malignant conditions, and many of their questions have yielded new technologies and areas of investigation, thus remaining highly relevant nearly 40 years after their initial asking. Moreover, continuing advances in our ability to measure physical properties such as absorbed light dose, photosensitizer concentration, tissue oxygen concentration and singlet oxygen production in real-time may allow for adaptive modification of light delivery during PDT on a fine scale in order to optimize treatment response. Finally, combining molecularly targeted drugs and novel photosensitizers has the potential to improve further the therapeutic index and extend the spectrum of clinical PDT far beyond what was imagined when that sentinel manuscript was written.

Origination: A Brief History of PDT

At the turn of the 20th century, Oscar Raab was a medical student working with Herman von Tappeiner on the toxicity of acridine dyes to malaria-causing protozoa. Raab astutely traced inconsistencies in results of experiments with acridine red and paramecia to variations in the level of ambient sunlight when the experiments were performed. While the use of light with a sensitizing agent had been described in medical literature dating back more than 3000 years, von Tappeiner and a dermatologist named Jesionek published the first report describing the use of 1% eosin and white light to successfully treat patients with basal cell carcinoma of the skin just 3 years after Raab's initial report. In the decade that followed, von Tappeiner's group determined that this "photodynamic" effect required the presence of a photosensitizer, light and oxygen to mediate cellular toxicity. Freiderich Meyer-Betz performed the first human trial of hematoporphyrin-mediated PDT by injecting himself with 200 mg of the drug and standing in sunlight. Over next 60 years, the photodynamic effect was studied intermittently while more sophisticated biomedical optics, laser light sources and novel porphyrin-based photosensitizers were developed. The interest in porphyrin-based

*From Shakespeare's *The Tempest* (II.i.245–254)

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drugs remained primarily in their tumor localizing properties for fluorescence diagnosis rather than in their ability to act as photosensitizers. Initially hematoporphyrin derivative (HpD) was created as a potential radiation sensitizer, but it was investigated in the 1960s for fluorescence-guided diagnosis for patients with malignancies of the esophagus, bronchus, uterine cervix and head and neck. However, HpD was found to have significant limitations due to suboptimal tumor sensitivity and specificity. Nevertheless, research groups at multiple institutions found that HpD and either white, or the more deeply penetrating red light, could be used effectively to treat mice bearing mammary, brain (glioma) or bladder tumors.

Arrival: A Landmark in Cancer Research

Building on this foundation, Dougherty and his colleagues at Roswell Park Cancer Institute (RPCI) reported the first large-scale trial of PDT in human cancers [1]. In total, 113 primary and metastatic skin tumors were treated in 25 patients with diagnoses ranging from malignant melanoma to mycosis fungoides to metastatic breast and endometrial cancers. Many of those tumors were recurrent or progressive after multiple cytotoxic chemotherapy agents and local ionizing radiotherapy. That study evaluated both tumor and normal tissue (skin) response and tested a variety of parameters thought to be critical to the efficacy of PDT and to influence its therapeutic index: the HpD dose was 2.5 or 5 mg/kg, the drug-light interval (DLI) ranged from 24 to 192 hours and the light dose was 120 J/cm^2 delivered in 1 to 6 fractions from an arc lamp with a 600 to 700 nm filter. A complete response was observed in an astounding 98/113 (88%) lesions, and only 3 tumors showed no response to therapy. Of the 98 complete responses, 96 maintained local control at 6 months. This study was the first to establish both the feasibility and efficacy of clinical PDT on a large scale; and it also demonstrated the ability of PDT to treat tumors successfully that were resistant to traditional therapies. Further analyses of PDT parameters showed that the optimal therapeutic index depended on the DLI, drug dose and attempted to estimate the effects of fluence rate, tissue optical properties/depth of light penetration and light scattering on PDT dose and efficacy. Since that article was published, decades of preclinical and clinical research have focused on understanding how these variables influence the efficacy and therapeutic index of PDT. Moreover, by demonstrating the feasibility and efficacy of PDT as a cancer treatment, that classic study by Dougherty and colleagues supported the clinical development of porphyrin-based photosensitizers and also stimulated the evolution of next-generation photosensitizers and novel light delivery devices and dosimetry techniques that are clinical employed with modern day PDT. One of PDT's attractions is comparative specificity of tumor effects over normal tissues.

Moving Forward: PDT as Non-Ionizing Radiotherapy

The classic study by Dougherty and colleagues was performed in patients with superficial, cutaneous cancers. A critical underpinning of that study is suggested by the name "photoradiation therapy." Like ionizing radiation therapy, PDT is fundamentally a localized treatment using electromagnetic energy, which has the intrinsic physical limitation of visible light that makes PDT best suited for tumors located at a depth of <1 cm from the radiation (light) source. Thus, in addition to cutaneous tumors, subsequent work from RPCI and other groups has focused on internal sites where light could be delivered endoscopically, such as

endobronchial, esophageal or bladder cancers or dysplasias, resulting in the currently approved indications for PDT in the United States, Canada and the European Union [2–3]. Also in parallel with methods for delivery of ionizing radiation therapy, methods have been developed to deliver light for intracavitary and interstitial applications. Intracavitary PDT has been developed as a method to treat microscopic residual disease following surgical resection of pleural or peritoneal malignancies [4] and is currently being evaluated in an NCI-sponsored randomized phase II trial of extended pleurectomy-decortication with or without PDT in patients with epithelioid malignant pleural mesothelioma (NCT02153229). In addition, intracavitary approaches are currently under clinical evaluation for intraoperative treatment of CNS, head and neck, breast, bladder and bile duct malignancies, including a NCI-sponsored randomized phase II trial of PDT vs surgical resection for patients with T1/T2 squamous cell carcinomas of the oral cavity (NCT02119728). In this respect, one particularly exciting approach merges fluorescence guided resection and PDT of microscopic residual disease, providing the opportunity to realize the full theranostic value of photosensitizers [3]. Finally, using fiber optics to deliver light through implanted catheters with techniques adapted from brachytherapy, interstitial PDT has been used to treat cancers in the head and neck, prostate, lung, pancreas and liver [3–5]. The only limitation of PDT is the imagination required to figure out how to introduce the light source where it is needed. This is why many of its future uses will require collaboration with surgical colleagues.

Lamp Posts Along the Way: PDT Dosimetry

Another theme from the initial RPCI clinical study was the realization that quantifying light is critical for the successful application of PDT. The combination of direct measurement in tissues and computational modeling foreshadowed the currently available techniques in explicit and implicit PDT dosimetry [3–5]. Initial attempts at explicit dosimetry relied on *ex vivo* measurements to estimate tumor and normal tissue photosensitizer levels combined with real-time monitoring of tissue light doses used non-isotropic (flat, incident light only) detectors. Newer methods have been developed to measure photosensitizer concentration using *in vivo* fluorescence that measures both incident and scattered light dose using isotropic detectors. In addition, computational methods are currently being evaluated to provide more accurate, potentially real-time PDT dosimetry which could reduce the operator dependence of the procedure itself [4–5]. Along with improved dosimetry methods, exciting advances in the area of light delivery such the fabrics woven from side-emitting optical fibers will continue to improve the efficacy and maximize the safety of PDT [6].

Towards New Horizons: Targeted PDT

The final critical determinant of PDT efficacy in the classic RPCI study is the time interval between photosensitizer administration and light delivery, fractionation of light delivery, and light fluence rate. Further work has borne out the hypothesis that the DLI can alter the type of damage to tumor and normal tissues, as well as the therapeutic index of PDT. For example, the preferential vascular damage that occurs when intravenous photosensitizers are used with relatively short DLI when the photosensitizer is primarily located within the vascular compartment (“vascular targeted PDT”) has been used to adapt PDT to the treatment of wet macular degeneration and may be useful in producing an anti-angiogenic

effect in cancer treatments [7]. For topically applied photosensitizers such as ALA and its derivatives, short DLI has been successfully applied as an antimicrobial therapy in the oral cavity or even using sensitizer application followed by exposure to normal sunlight ("daylight PDT") to reduce normal tissue toxicity during treatment of cutaneous malignancies [8–9]. The effects of fractionation and light fluence rate are similarly extensive, providing opportunities to adapt PDT to minimize the impact of intrinsic cancer cells and PDT-induced tumor-stroma growth and survival signaling, while maximizing induction of host anti-tumor immunity [10]. Further targeting of tumor or stromal biology using molecularly targeted therapy in conjunction with PDT can further augment the beneficial effects of optimizing the DLI, light fractionation and fluence rate on cancer therapy and especially in treatment of premalignant lesions including in situ carcinomas.

End of the beginning: Summary and Conclusions

The landmark study by Dougherty and his colleagues at RPCI launched the modern practice of clinical PDT. The questions raised by this study anticipated much of the preclinical and clinical research and development that have occurred in the nearly 40 years since its publication. Going forward, with light delivery, dosimetry and photosensitizer technologies more fully developed, and as encouraging clinical findings of PDT are being attempted to be validated in randomized clinical trials, the impact of the classic study by Dougherty et al. is likely to continue to grow.

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