

## COMMENTARY

# Clinical Applications of Photodynamic Therapy

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Photodynamic therapy (PDT) is an important tool in the treatment of cancer. In almost half a century since the first report,<sup>1</sup> it has reached a significant level of maturity and has achieved impressive successes. A number of innovative and instructive studies were presented and discussed at the workshop on “Molecular pathways in the response of tumors to photodynamic therapy.” There were also examples of notable personal successes in the clinical application of these approaches, which highlighted the importance of this strategy in cancer treatment.

Some successful applications of PDT have been presented and discussed. One such example by Dr. Michela Magaraggia (Padova, Italy) was its novel use in water disinfection for the prevention and treatment of infectious diseases.<sup>2,3</sup>

Photodynamic therapy (PDT) has been applied with considerable success in dermatology.<sup>4–8</sup> There were a number of presentations on first-hand experience in dermatological applications of PDT in the clinic by Doctors Pietro Cappugi (Firenze, Italy), Anne

Moor (Wedel, Germany), and Dennis Linder (Padova, Italy).

Photofrin (porfimer sodium) is an oligomer of up to eight porphyrins. It is photosensitized by red light at 630 nm and is employed for PDT and radiation therapy in palliative treatment of obstructing endobronchial non-small-cell lung carcinoma and obstructing esophageal cancer.<sup>9–11</sup> In his presentation, Dr. Luigui Corti (Padua, Italy) described results of some of his clinical studies in the photodynamic therapy of bronchial cancer.<sup>12–13</sup>

Another porphyrin derivative, Verteporfin, is a benzoporphyrin derivative employed as a photosensitizer in ophthalmological PDT. It is used for blocking abnormal blood vessels associated with some conditions like the wet form of macular degeneration.<sup>14–18</sup> The photosensitizer accumulates in the abnormal blood vessels and on illumination by red light of 693-nm wavelength in the presence of oxygen, generates very reactive short-lived singlet oxygen as well as other oxygen radicals. This causes local damage to the endothelium and results in blockage of the vessels. Dr. Daniele

Veritti (Udine, Italy) described his successful first hand clinical experience of using Verteporfin in ophthalmological treatments.<sup>19</sup>

Novel and original research studies aimed at elucidating molecular mechanisms of action and or devising therapeutic improvements or new applications were presented (see report by Bonavida and Atassi in this issue). A number of the basic studies employed established cell lines to study the effects of a certain drug or to elucidate the mechanism of action a certain application. It should be cautioned that studies of cell lines, although an extremely useful tool, might not yield the ultimate conclusion that will be entirely relevant to the *in vivo* situation. As they develop in culture, cells change in many respects relative to their *in vivo* origin. The changes might include cell markers and the expression of important structural and/or functional proteins and genes. So their reaction to foreign agents or stimulants might not necessarily mimic the behavior of the original tumors. Studies should wherever feasible be confirmed by studies on primary tumor cell lines and finally by *in vivo* studies.

Protoporphyrin is the agent of choice for photodynamic therapy. This compound is insoluble in aqueous solvents and it is often necessary to dissolve it in an organic solvent and transfer it in small amounts into an aqueous solvent for PDT studies. This creates a problem because it not easy to know the exact amount that is retained in solution under the conditions of extreme dilution. Some studies were aimed at the preparation of soluble derivatives of protoporphyrin by attachment of side chains that have desirable charge properties while keeping the protoporphyrin ring structure intact. This is a rational approach that has found useful applications. Other studies endeavored to attach the protopor-

phyrin ring to nanomolecular carriers. Some of these carriers could not be metabolized or cleared in the kidney so they are likely to be deposited, and accumulate, in the liver and might, if applied frequently, cause impairment of normal liver function.

The ideal way to target the therapeutic agent to the tumor would be to attach the agent to a monoclonal antibody (mAb) that is specific against a tumor-associated marker. This is obviously a labor-intensive effort. It requires considerable work to identify a tumor-associated marker, and then use this protein or a synthetic peptide representing a suitable epitope(s) of this protein as an antigen to make specific antibodies with good affinity and then prepare an mAb that will bind specifically to the protein marker. Having achieved this, the mAb is then used as a carrier for the anti-tumor therapeutic agent. This approach has the advantage of specificity and selectivity. Because the therapeutic agent is carried by the mAb it will be targeted to the tumor with an exquisite specificity that is determined by that of the mAb. This will make it possible to use a lower general dose of the therapeutic agent than would otherwise be needed. One elegant paper by Dr. Pål Kristian Selbo (Lysaker, Norway) and his colleagues<sup>20</sup> employed this strategy in their studies on photochemical internalization of cancer stem cells.

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