brief oncogene inactivation might be sufficient to induce sustained loss of a neoplastic phenotype under some circumstances. Tumours can escape the dependence on oncogenes, apparently by acquiring new genetic events. Collectively, these results indicate that cancer is caused by genetic events that occur in a requisite epigenetic context. So, cancer might be treatable by inactivating oncogenes or by inducing the differentiation of tumours. The current challenge is to define when oncogenes will be good therapeutic targets and define how specific differentiative states provide the permissive epigenetic contexts to support neoplasia. By understanding how genetic events sustain tumorigenesis in specific epigenetic contexts, we might be able to treat cancer through the development of drugs that inactivate oncogenes or revoke permissive epigenetic states that are responsible for tumorigenesis.

Dean W. Felsher is at the Division of Oncology, Departments of Medicine and Pathology, Stanford University, 269 Campus Drive, CCSR 1105, Stanford, California 94305-5151, USA.
e-mail: dfelsher@stanford.edu

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Online links

DATABASES
The following terms in this article are linked online to:
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TIMELINE

Photodynamic therapy for cancer

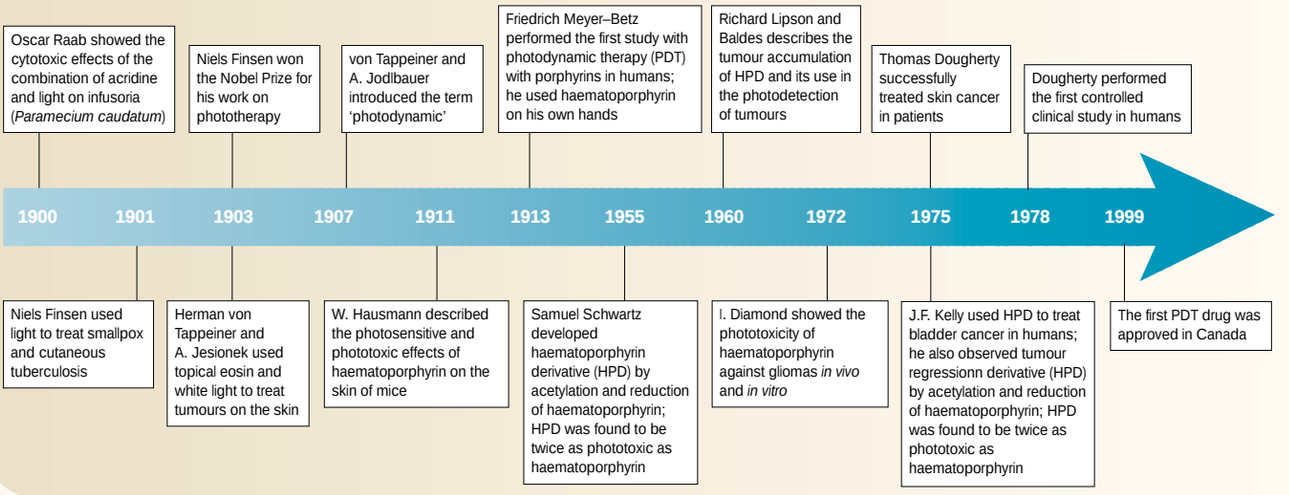
Dennis E.J.G.J. Dolmans, Dai Fukumura and Rakesh K. Jain

The therapeutic properties of light have been known for thousands of years, but it was only in the last century that photodynamic therapy (PDT) was developed. At present, PDT is being tested in the clinic for use in oncology — to treat cancers of the head and neck, brain, lung, pancreas, intraperitoneal cavity, breast, prostate and skin. How does PDT work, and how can it be used to treat cancer and other diseases?

Light has been used as therapy for more than three thousand years[1,2]. Ancient Egyptian, Indian and Chinese civilizations used light to treat various diseases, including psoriasis, rickets, vitiligo and skin cancer[3]. At the end of the nineteenth century in Denmark, Niels Finsen further developed 'phototherapy' — or the use of light — to treat diseases. He found that red-light exposure prevents the formation and discharge of smallpox pustules and can be used to treat this disease[4]. He also used ultraviolet light from the sun to treat cutaneous tuberculosis. This was the beginning of the modern light therapy, and, in 1903, Finsen was awarded a Nobel Prize for his discoveries (see TIMELINE).

More than 100 years ago, researchers also observed that a combination of light and certain chemicals could induce cell death. In 1900, German medical student Oscar Raab reported that certain wavelengths were lethal to infusoria — including a species of *Paramecium* — in the presence of acridine[5]. In the same year, a neurologist in France named J. Prime found that epilepsy patients who were treated with oral EOSIN developed DERMATITIS in sun-exposed areas[6]. Later, Herman Von Tappeiner and A. Jesionek treated skin tumours with topically applied eosin and white light in 1903 (REF. 7); they described this phenomenon as 'PHOTODYNAMIC ACTION'[8].

Timeline | History of photodynamic therapy (1900–present)



Experiments to test combinations of reagents and light led to modern photodynamic therapy (PDT). PDT involves two individually non-toxic components that are combined to induce cellular and tissue effects in an oxygen-dependent manner (FIG. 1). The first component of PDT is PHOTOSENSITIZER — a photosensitive molecule that localizes to a target cell and/or tissue. The second component involves the administration of light of a specific wavelength that activates the sensitizer. The photosensitizer transfers energy from light to molecular oxygen, to generate reactive oxygen species (ROS). These reactions occur in the immediate locale of the light-absorbing photosensitizer. Therefore, the biological responses to the photosensitizer are activated only in the particular areas of tissue that have been exposed to light. Other photochemical reactions that do not use oxygen as an intermediate[9] — for example, photoaddition to DNA — have also been developed. These reactions are called 'photochemotherapy'. One photochemotherapeutic, called 'psoralens', has been combined with ultraviolet A to treat psoriasis, vitiligo and to enhance immunotherapy[10].

The most extensively studied photosensitizers so far are porphyrins, which were identified in the mid-nineteenth century. These compounds contain a porphin structure — four pyrrole rings connected by methine bridges in a cyclic configuration — along with a side chain that is usually metallic. For example, the combination of iron with a porphin structure forms haem. W. Hausmann performed the first studies with these reagents. He treated paramecium and red blood cells with haematoporphyrin and light, and reported that this combination killed the cells. In addition, he reported skin reactions in mice that were exposed to light after haematoporphyrin administration[11]. In 1913, the German scientist Friedrich Meyer–Betz was the first to treat humans with porphyrins, testing the effects of 200 mg of haematoporphyrin on his own skin[12]. He observed swelling and pain specifically in light-exposed areas.

In the 1960s, Richard Lipson and colleagues initiated the modern era of PDT at the Mayo Clinic[13,14]. These studies involved a compound that was developed by Samuel Schwartz called 'haematoporphyrin derivative' (HPD)[15]. To prepare this derivative, crude haematoporphyrin was treated with acetic and sulphuric acids, filtered and then neutralized with sodium acetate. The precipitate was then resolved in saline to produce HPD. Lipson and E.J. Baldes then showed that HPD localized to tumours, where it emitted fluorescence. Because this derivative could also be administered at much smaller doses than crude haematoporphyrin, it held promise as a diagnostic tool[16]. The mechanisms by which photosensitizers such as HPD selectively accumulate in tumours are complex and not fully understood. It is presumably because of the high vascular permeability of the agents, as well as their affinity for proliferating endothelium and the lack of lymphatic drainage in tumours[17,18].

The therapeutic application of PDT to patients with cancer took a long time to develop since the first experiments of Von Tappeiner and Jesionek were carried out in 1903. In 1972, I. Diamond and colleagues postulated that the combination of the tumour-localizing and tumour-phototoxic properties of porphyrins might be exploited to kill cancer cells[19]. *In vivo* studies revealed that PDT delayed the growth of gliomas that were implanted in rats. Tumour growth was suppressed for 10–20 days, but eventually, viable areas from deeper regions of the tumours began growing again. A significant breakthrough occurred in 1975 when Thomas Dougherty and co-workers reported that administration of HPD and red light completely eradicated mammary tumour growth in mice[20]. In the same year, J.F. Kelly and co-workers reported that light activation of HPD also eliminated bladder carcinoma in mice[21].

In 1976, Kelly and co-workers initiated the first human trials with HPD — in patients with bladder cancer[22]. Five patients were diagnosed with the cancer using HPD. It was also used to treat one patient with recurrent bladder

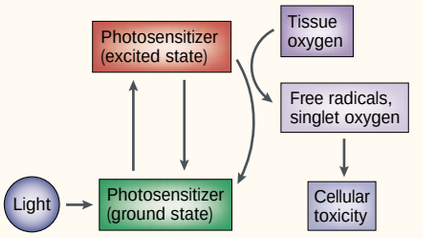


Figure 1 | **Mechanism of action of photodynamic therapy (PDT).** PDT requires three elements: light, a photosensitizer and oxygen. When the photosensitizer is exposed to specific wavelengths of light, it becomes activated from a ground to an excited state. As it returns to the ground state, it releases energy, which is transferred to oxygen to generate reactive oxygen species (ROS), such as singlet oxygen and free radicals. These ROS mediate cellular toxicity.

Table 1 | Photosensitizers for malignant diseases

Sensitizer	Trade name	Potential indications	Activation wavelength
HPD (partially purified), porfimer sodium	Photofrin	Cervical*, endobronchial*, oesophageal*, bladder* and gastric cancers*, and brain tumours	630 nm
BPD-MA	Verteporfin	Basal-cell carcinoma	689 nm
m-THPC	Foscan	Head and neck tumours*, prostate and pancreatic tumours	652 nm
5-ALA	Levulan	Basal-cell carcinoma, head and neck, and gynaecological tumours Diagnosis of brain, head and neck, and bladder tumours	635 nm 375–400 nm
5-ALA-methylesther	Metvix	Basal-cell carcinoma*	635 nm
5-ALA benzylesther	Benzvix	Gastrointestinal cancer	635 nm
5-ALA hexylesther	Hexvix	Diagnosis of bladder tumours	375–400 nm
SnET2	Purlytin	Cutaneous metastatic breast cancer, basal-cell carcinoma, Kaposi's sarcoma, prostate cancer	664 nm
Boronated protoporphyrin	BOPP	Brain tumours	630 nm
HPPH	Photochlor	Basal-cell carcinoma	665 nm
Lutetium texaphyrin	Lutex	Cervical, prostate and brain tumours	732 nm
Phthalocyanine-4	Pc 4	Cutaneous/subcutaneous lesions from diverse solid tumour origins	670 nm
Taporfin sodium	Talaporfin	Solid tumours from diverse origins	664 nm

*Indications that are registered in one or more countries (all other indications are in development). 5-ALA, 5-aminolevulinic acid; BPD-MA, benzoporphyrin derivative-monoacid ring A; HPD, haematoporphyrin derivative; HPPH, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-alpha; mTHPC, meta-tetrahydroxyphenylchlorin; SnET2, tin ethyl etiopurpurin.

carcinoma who had failed transurethral resections, radiotherapy and chemotherapy. In this patient, HPD slowed tumour growth, and tumour necrosis was seen in the areas that received PDT. In a second study by Dougherty *et al.*, 25 patients with a total of 113 primary or secondary skin tumours were treated with HPD. A complete response was observed in 98 tumours, a partial response was observed in 13 tumours and 2 tumours were found to be treatment resistant[23]. Following the preliminary successes in treating bladder and skin tumours, Y. Hayata and colleagues used PDT to treat obstructing lung tumours[24]. Bronchoscopic analysis revealed tumour growth delay in most patients, but only one out of fourteen patients was cured.

In 1984, J.S. McCaughan and colleagues used PDT to treat patients with oesophageal cancer[25], O.J. Balchum and colleagues used PDT to treat patients with lung cancer[26] and, 1 year later, Y. Hayata and colleagues used PDT to treat patients with gastric carcinoma[27]. All of these studies showed promising responses in early-stage patients, so PDT was recommended for patients with early-stage cancers that were inoperable, due to other complications. Patients with breast cancer[28–30], gynaecological tumours[31–33], intraocular tumours[34–36], brain tumours[37–40], head and neck tumours[41,42], colorectal cancer[43,44], cutaneous malignancies[45,46], intraperitoneal tumours[47], mesothelioma[48], cholangiocarcinoma[49] and pancreatic cancer[50] were subsequently treated with PDT. However, this technique has only shown limited success in further studies, due to issues surrounding specificity and potency of photosensitizers. Another confounding factor is that PDT has been tested largely in patients with advanced-stage diseases that are refractory to other treatments. In such cases, a local effect cannot usually significantly alter the outcome of a systemic disease[18]. More selective and potent sensitizers have been developed, and are now under investigation in clinical trials (TABLE 1). With this new line of drugs, as well as with better localization methods[18] and improved protocols and equipment, the efficacy of PDT might be improved[51].

Mechanism of action

One advantage of PDT is that the photosensitizer can be administered by various means, such as by intravenous injection or topical application to the skin. However, these affect its biodistribution. Because biodistribution changes over time, the timing of light exposure is another way to regulate the effects of PDT. Following the absorption of light (photons), the sensitizer is transformed from its ground state (singlet state) into a relatively long-lived electronically excited state (triplet state) via a short-lived excited singlet state[52]. The excited triplet can undergo two kinds of reactions (FIG. 2). First, it can react directly with a substrate, such as the cell membrane or a molecule, and transfer a hydrogen atom (electron) to form radicals. These radicals interact with oxygen to produce oxygenated products (type I reaction). Alternatively, the triplet can transfer its energy directly to oxygen, to form singlet oxygen — a highly ROS (type II reaction). Because the effects of almost all PDT drugs are oxygen dependent, photosensitization typically does not occur in anoxic areas of tissue. *In vivo* studies showed that induction of tissue hypoxia, by clamping, abolished the PDT effects of porphyrins[53].

Both type I and type II reactions occur simultaneously, and the ratio between these processes depends on the type of sensitizer used, the concentrations of substrate and oxygen, as well as the binding affinity of the sensitizer for the substrate. Because of the high reactivity and short half-life of the ROS, only cells that are proximal to the area of the ROS production (areas of photosensitizer localization) are directly affected by PDT[54]. The half-life of singlet oxygen in biological systems is <0.04 μs, and, therefore, the radius of the action of singlet oxygen is <0.02 μm[54]. The extent of photodamage and cytotoxicity is multifactorial and depends on the type of sensitizer, its extracellular and intracellular localization, the total dose administered, the total LIGHT EXPOSURE DOSE, light FLUENCE RATE, oxygen availability, and the time between the administration of the drug and light exposure. All of these factors are interdependent.

PDT's effects on tumours

It is now known that there are three main mechanisms by which PDT mediates tumour destruction[17,18]. In the first case, the ROS that is generated by PDT can kill tumour cells directly. PDT also damages the tumour-associated vasculature, leading to tumour infarction. Finally, PDT can activate an immune response against tumour cells. These three mechanisms can also influence each other. The relative importance of each for the overall tumour response is yet to be defined. It is clear, however, that the combination of all these components is required for long-term tumour control.

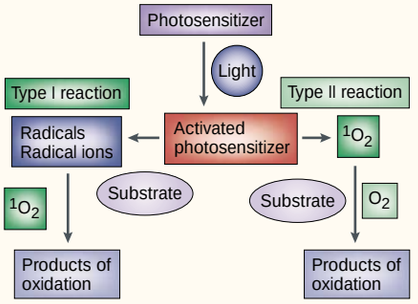


Figure 2 | **Type I and type II reaction in photodynamic therapy (PDT).** There are two types of reaction during PDT. Following the absorption of light, the sensitizer is transformed from its ground state into an excited state. The activated sensitizer can undergo two kinds of reaction. First, it can react directly either with the substrate, such as the cell membrane or a molecule, transferring a hydrogen atom to form radicals. The radicals interact with oxygen to produce oxygenated products ($^1O_2$) (type I reaction). Alternatively, the activated sensitizer can transfer its energy directly to oxygen, to form singlet oxygen ($^1O_2$) — a highly reactive oxygen species. These species oxidize various substrates (type II reaction).

Direct tumour-cell killing. In vivo exposure of tumours to PDT has been shown to reduce the number of clonogenic tumour cells, through direct photodamage[55]. However, complete tumour eradication is not always fully realized by this mechanism alone for many reasons. One reason is non-homogenous distribution of the photosensitizer within the tumour. Furthermore, in 1995, Mladen Korbelik and colleagues showed that both intravenously administered photosensitizer accumulation and the level of tumour-cell killing decrease with the distance of tumour cells from the vascular supply[56].

Another parameter that can limit direct tumour-cell destruction is the availability of oxygen within the tissue that is targeted by PDT. Oxygen shortage can arise as a result of the photochemical consumption of oxygen during the photodynamic process, as well as from the immediate effects of PDT on the tissue microvasculature. Rapid and substantial reduction in the tissue oxygen tension during and after illumination of photosensitized tissue have been reported[57,58]. Depending on the localization of the photosensitizer at the time of illumination, oxygen tension can increase transiently[59]. Although the development of microvascular damage and hypoxia after PDT have been shown to contribute to the long-term tumour response, the reductions in oxygen that occur during PDT can limit the response. There are two ways to overcome this problem. One is to lower the light fluence rate to reduce oxygen consumption rate, and the other is to fractionate the PDT light delivery to allow re-oxygenization of the tissue[60,61]. The extent of modulation by fluence rate is dependent on the localization of the photosensitizer[62].

Vascular damage. The viability of tumour cells also depends on the amount of nutrients supplied by the blood vessels. In turn, formation and maintenance of blood vessels depend on growth factors produced by tumour or host cells[63,64]. Targeting the tumour vasculature is therefore one promising approach to cancer treatment. In the past 15 years, there have been a number of reports of PDT causing microvascular collapse[65–68], leading to severe tissue hypoxia and anoxia[69–71]. As early as 1989, Barbara Henderson and colleagues showed in a fibrosarcoma mouse model that Photofrin-based PDT (Photofrin is a photosensitizer produced by Axcan Pharma, Montreal, Canada) induced vascular shutdown, limiting the oxygen supply to the tumour[72]. Pre-clinical *in vivo* studies that were performed last year with the photosensitizer MV6401 — a pyropheophorbide derivative (Miravant Medical Technologies, Santa Barbara, California) — showed a biphasic vascular response following PDT. The first, immediate response was vasoconstriction. After three hours, a second, long-term response, characterized by thrombus formation, occurred[68]. This response could be inhibited with heparin. These vascular effects were associated with a delay in tumour growth. Previous studies with other photosensitizers, such as a benzoporphyrin derivative (BPD)[67], HPD[65] and Photofrin[66] also reported vascular constriction, thrombus formation and inhibition of tumour growth. On the other hand, expression of vascular endothelial growth factor (VEGF) and cycloxygenase (COX)-2 — both potent angiogenic factors — were upregulated during PDT (REFS 73, 74; and D.E. Dolmans *et al.*, unpublished observations). These effects were presumably due to the ROS formation and hypoxia that was induced by PDT. Further studies are required to determine the long-term effects of PDT on tumour vasculature.

Immune response. Studies in the late 1980s and early 1990s also reported infiltration of lymphocytes, leukocytes and macrophages into PDT-treated tissue, indicating activation of the immune response[52,76]. Differences in the nature and intensity of the inflammatory reaction between normal and cancerous tissues could contribute to the selectivity of PDT-induced tissue damage. The inflammatory process is mediated by factors such as vasoactive substances, components of the complement and clotting cascades, acute-phase proteins, proteinases, peroxidases, ROS, leukocyte chemoattractants, cytokines, growth factors and other immunoregulators. The inflammatory cytokines interleukin (IL)-6 and IL-1, but not tumour necrosis factor-α (TNF-α), have been shown to be upregulated in response to PDT[77]. In 1996, Wil de Vree and colleagues also reported that PDT activated neutrophil accumulation, which slowed tumour growth[78]. Depletion of neutrophils in tumour-bearing mice decreased the PDT-mediated effect on tumour growth[78].

Box 1 | Targeting delivery systems for photodynamic therapy

The rationale for the use of molecular delivery systems for photosensitizers is similar to that for the delivery of chemotherapeutics and toxins. Carrier-mediated delivery allows increased accumulation of sensitizer at the targeted site and the use of photosensitizers that have efficient photochemistry but cannot accumulate in tumours adequately. Carriers therefore broaden the clinical repertoire of sensitizers, and minimize the amount of precision that is needed in light delivery. Furthermore, the sensitizer does not need to dissociate from carriers for activation to occur, and additional target specificity can be achieved by controlling the location at which light activates the drug. Various delivery systems have been tested in preclinical models. Photoimmunotargeting uses monoclonal antibodies that recognize tumour antigens. For example, chlorin e6-monoethylenediamine monoamide (CMA), haematoporphyrin or meta-tetrahydroxyphenylchlorin (mTHPC or Foscan) can be coupled to a selective monoclonal antibody[119–121]. Ligands against receptors that are upregulated in tumour cells could be another delivery vehicle. For example, tumour cells that express the low-density lipoprotein (LDL) receptor have been shown to internalize a LDL-coupled photosensitizer[122–124]. Another strategy is to target the sensitizer to the peripheral benzodiazepine receptor[125] or oestrogen receptor in hormone-dependent tumours[126]. Finally, liposomes and immunoliposomes can be used in conjunction with photosensitizers[127,128]. However, the main problem is that many physiological barriers, such as spatially and temporally heterogeneous blood flow and vascular permeability, can still hinder the delivery of these sensitizers to tumours[82,83].

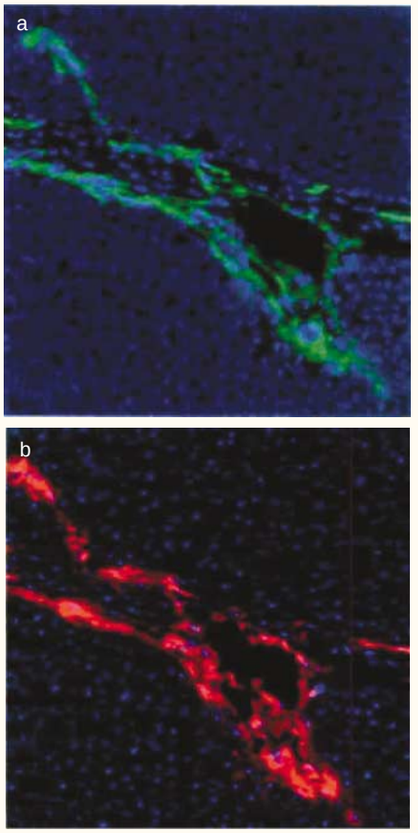


Figure 3 | **Localization of a photosensitizer to vascular endothelial cells. a** | Colour composite image of staining for vascular endothelial cells (green) of the tumour, which are surrounded by non-vascular cells (nucleus, blue) (×20 magnification). **b** | The photosensitizer MV6401 (red) localizes specifically to vascular endothelial cells, after intravenous injection into a severe combined immunodeficient mouse with MCaIV mouse breast cancer. Reproduced with permission from REF. 84.

In 1996, Mladen Korbelik and colleagues compared the long-term effects of PDT on tumour growth in normal Balb/C and immunodeficient mice. Whereas short-term tumour responses to Photofrin PDT were similar, long-term effects were quite different, as tumour recurrence occurred more frequently in the immunocompromised mice. This effect was reversed by bone-marrow transplants from immunocompetent Balb/C donors. These results indicate that, whereas the direct effects of PDT can destroy the bulk of the tumour, the immune response is required to eliminate the surviving cells[79].

In 1999, Korbelik and colleagues reported that PDT generated tumour-sensitized immune cells that could be recovered from lymphoid sites distant to the treated tumour at different time intervals after PDT[80]. An interesting observation was also made by Barbara Henderson and colleagues, who reported that a tumour-cell lysate that was isolated following PDT with Photofrin could be used to vaccinate mice against the development of further tumours, indicating the induction of tumour-specific immunity[81]. This vaccination approach has been shown to be more effective at activating an immune response than lysates made from tumours that were exposed to ultraviolet or ionizing irradiation. These PDT vaccines seem to induce a cytotoxic T-cell response that involves induction of IL-12 expression. Studies with PDT and tumour-cell lysates indicate that PDT could have potential as a systemic immune therapy[81]. Further experiments are required to determine whether similar results can be obtained in patients who receive PDT.

Factors that affect PDT efficacy

Tumour localization of the photosensitizer is an important factor that determines PDT efficacy. Researchers therefore set out to improve the localization of the photosensitizer to specific regions of the tumour tissue (BOX 1). In the past years, a number of more selective photosensitzers have been developed. For example, MV6401 has been shown to selectively localize to the tumour vasculature[68]. Drug localization is known to be determined by vascular permeability and interstitial diffusion, which depend on molecular size, configuration, charge, and hydrophilic or lipophilic property of the compound, as well as physiological properties of blood vessels[82]. Binding of the drug with various components of the tissue can also influence its transport and retention in tumours[82,83].

The interval between the sensitizer administration and light exposure was also another key factor in determining PDT efficacy. When a short interval (15 minutes) was allowed between drug and light administration, the sensitizer predominantly accumulated in the vascular compartment. This resulted in vascular stasis and thrombus formation, followed by indirect tumour-cell killing. Conversely, a longer interval (4 hours) between intravenous drug injection and light administration resulted in MV6401 localization to the extravascular compartment of the tumour, due to relatively slow leakage from the vasculature and interstitial diffusion[84] (FIG. 3). In the treatment of most cancers, the interval between drug and light administration is typically longer — in the order of 24–72 hours — in the cases of Photofrin[85] or meta-tetrahydroxyphenylchlorin (mTHPC, or Foscan, Biolitec Pharma, Scotland, UK)[86]. So, different time intervals between photosensitizer and light administration destroy tumour cells by different mechanisms and have different consequences[59].

In the past year, PDT protocols have therefore been modified to optimize targeting of both the vascular and tumour-cell compartments[84]. Administration of photosensitzers at multiple time intervals before light activation (fractionated drug-dose PDT), was found to be the most effective way to target both tumour blood vessels and tumour cells. Fractionated drug-dose PDT regimens were reported to result in a superior therapeutic effect, compared to single-dose regimens such as anti-vascular PDT or anti-tumour-cell PDT, and were able to induce long-term tumour growth control[84]. This is one more example that the most effective way to attack a tumour is through the targeting of several compartments.

Another way to direct the photosensitizer to a certain cell type or compartment is to use specific targeting carriers, such as conjugated antibodies directed to tumour-associated antigens or vascular antigens, such as the ED-B domain[87]. Since the mid-1990s, photosensitizers have been developed that can localize to the mitochondria, plasma membrane, lysosomes and nuclei[88]. The site of action within a cell also contributes to the efficacy of PDT[89]. In fact, the mitochondria have been proposed to be some of the most effective subcellular targets for photodamage[17,51]. These factors are important to consider when combining PDT with other treatment modalities, such as therapeutics that are designed to target different subcellular regions or cell functions[90].

Clinical applications of PDT

PDT was first approved in 1993 in Canada, using the photosensitizer Photofrin for the prophylactic treatment of bladder cancer. This is the most commonly used photosensitizer in the clinic today. The development of Photofrin arose from an initial discovery in 1983 by Thomas Dougherty, who showed that crude haematoporhyrin contains a range of different porphyrins. When these were converted to HPD by acetylation, additional porphyrins were produced, such as protoporphyrin and hydroxyethylvinyldeuteroporphyrin[91]. The following year, he proposed that the active component of HPD was composed of two porphyrin units linked by an ether bond[92], and he named this compound dihaematoporphyrin ether (DHE). Photofrin is partially purified HPD — a mixture of mono-, di- and oligomers that all contain the porphyrin moiety.

Table 2 | Type of cancer and approved drugs (2003)

Disease	Drug	Country
Pre-cancer		
Actinic keratosis	Levulan, Metvix	EU
Barrett's oesophagus	Photofrin	EU, USA
Cervical dysplasia	Photofrin	Japan
Cancer		
Basal-cell carcinoma	Metvix	EU
Cervical cancer	Photofrin	Japan
Endobroncheal cancer	Photofrin	Canada, Denmark, Finland, France, Germany, Ireland, Japan, The Netherlands, UK, USA
Oesophageal cancer	Photofrin	Canada, Denmark, Finland, France, Ireland, Japan, The Netherlands, UK, USA
Gastric cancer	Photofrin	Japan
Head and neck cancer	Foscan	EU
Papillary bladder cancer	Photofrin	Canada

Photodynamic therapy has also been undertaken in other countries with haematoporphyrin derivative and porphyrin mixtures (China and India), and phthalocyanines (Russia and India). EU, European Union; UK, United Kingdom; USA, The United States.

The development of Photofrin was a breakthrough in PDT research, and this photosensitizer holds the largest number of approvals for clinical use (TABLE 1). Subsequent approvals for PDT with Photofrin were obtained in the Netherlands and France for the treatment of advanced-stage lung cancer, in Germany for the treatment of early-stage lung cancer, in Japan for early-stage oesophageal, gastric and cervical cancer, as well as cervical dysplasias, and in the United States for advanced oesophageal cancer (TABLE 2).

Although Photofrin is the most commonly used photosensitizer, there are several limitations of this compound. First, it consists of about 60 compounds and therefore it is difficult to reproduce its composition. Although the compound has a useful absorption maximum of 630 nm, its molar absorption coefficient at this wavelength is low (1,170 $M^{-1}cm^{-1}$). Therefore, high concentrations of sensitizer and light must be delivered to the tumour. Furthermore, Photofrin is not very selective for tumour tissue. Orenstein and colleagues[93] reported low tumour to normal tissue ratios of Photofrin uptake in C26 colon-carcinoma-bearing mice. Finally, Photofrin causes long-lasting cutaneous photosensitivity, as it is absorbed by the skin[94]. For this reason, patients who have been treated with Photofrin have to avoid sunlight for 4–6 weeks.

So, significant efforts have been invested in the development of new sensitizers. In particular, there was a need for new compounds that absorb light at longer wavelengths (to facilitate tissue penetration of the light), compounds with greater tumour specificity and compounds with less skin photosensitivity. To this end, many other sensitizers have recently been developed and have entered clinical trials. Foscan is another photosensitizer that is now approved for the treatment of head and neck cancer. This chlorin photosensitizer[95] requires very low drug doses (as little as 0.1 mg/kg body weight) and light doses (as low as 10 J/cm^2) for efficacy. However, significant complications have also been observed because of its high potency[96]. PDT with 5-aminolevulinic acid (5-ALA, or Levulan, DUSA Pharma, Toronto, Canada) and 5-ALA methylesther (Metvix, Photocure, Oslo, Norway) are approved for treating actinic keratosis and basal-cell carcinoma of the skin, by topical application followed by blue or red light exposures, respectively.

Other developments in PDT

As well as the photodynamic effect that occurs after light administration, these agents also produce fluorescence, which can be used to detect tumours (FIG. 3). Haematoporphyrins, porphyrins, HPD and ALA-derivatives are all being tested for use in tumour detection. The first successful studies on photodetection were carried out in 1955 by Rassmussan-Taxdal and colleagues, who treated cancer patients with haematoporphyrin hydrochloride and were able to identify tumour cells during histological examination[97]. In the early 1960s, Richard Lipson went on to use HPD to localize tumours in patients undergoing bronchoscopy or oesophagoscopy for suspected malignant diseases[14,16]. In patients with these disorders, Photofrin was administered intravenously and the fluorescence was monitored with an endoscope or bronchoscope. Squamous-cell carcinoma showed increased fluorescence and more-invasive tumours showed increased contrast[98]. In the mid-1990s, J.C. Kennedy and colleagues reported successful treatment of skin disorders with topically administered 5-ALA[99]. This relatively new approach of locally administered PDT has been applied in the treatment and detection of superficial lesions[100,101]. 5-ALA has also been used to guide the surgical resection of glioblastoma multiforme[102]. Photodetection might also be used to detect and treat pre/early-malignant lesions, such as dysplasia or carcinoma *in situ* within Barrett's oesophagus[103,104]. PDT can also be used to enhance the delivery of membrane-impermeable drugs to the cytosol of target cells by the technique called photochemical internalization[105].

PDT in other diseases. Today, the most popular application of PDT is in the treatment of age-related macular degeneration and other eye diseases that are related to neo-vascularization[106]. In 1999, Verteporfin (Novartis Inc., Basel, Switzerland) was approved in Canada[107]. Later, approval was granted in many other countries, including in the United States in 2000. As well as the treatment and detection of cancer and pre-cancerous lesions, and the use of PDT in ophthalmology, this strategy has been applied in cardiovascular diseases, dermatology and rheumatology. Paolo Ortu and colleagues pioneered the

Glossary

DERMATITIS
Inflammation of the skin.

EOSIN
The first photosensitizer used in photodynamic therapy by von Tappeiner.

FLUENCE RATE
The radiant energy incident per second across a sectional area of irradiated spot (power per unit area of light given in watts per square meter, W/m^2; 1 W = 1 J/s).

LIGHT EXPOSURE DOSE
The total energy of exposed light across a sectional area of irradiated spot (energy per unit area of exposed light, in joules per square meter, J/m^2). The energy content of light is proportional to the wavelength of absorption.

PHOTODYNAMIC ACTION
The reaction of cells to a chemical reagent (or photosensitizer), light and oxygen.

PHOTOSENSITIZER
A chemical that is required for photodynamic action. A photosensitizer transfers energy from the light to generate reactive oxygen species. Photofrin is the most widely used photosensitizer so far.

development of PDT for the treatment of arteries with intimal hyperplasia[108]. Other ongoing studies include PDT after stent implantation[109]. In dermatology, PDT is used to treat diseases such as psoriasis and scleroderma[110,111]. In the rheumatology field, PDT is being tested to treat arthritis[112]. Finally, PDT is going back to its origins in microbiology and being used to target microorganisms[113,114].

Future directions

PDT has been around for the past 100 years and has been an experimental clinical modality for the past two decades. In America, Asia and Europe, several photosensitizers have been approved for clinical use. Overall, PDT has the potential of being a palliative therapy or a primary therapy, depending on the specific indications.

Researchers are now investigating the ability to improve the tumour specificity of photosensitizers by conjugating them to tumour-associated antibodies. This approach has been used successfully to treat cancer in preclinical models[115], and also to treat angiogenesis-related diseases of the eye[116]. However, there are problems associated with the use of large molecules (monoclonal antibodies) in PDT. These include complicated synthesis, transport barriers[82,83,117] and potential toxicity.

In the future, it is likely that PDT will continue to be used as a stand-alone modality or in combination with chemotherapy, surgery, radiotherapy or other new strategies, such as anti-angiogenic therapy[73]. Other ways to improve PDT include the development of new photosensitizers, as well as the optimization of PDT protocols such as fractionation of light[118] or drugs[84]. Well-designed clinical trials that involve selectively localized photosensitizers and convenient light sources will also improve the prospects for the use of PDT in cancer and other diseases.

Edwin L. Steele Laboratory for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.
Correspondence to D.F. and R.K.J.
e-mails: dai@steele.mgh.harvard.edu; jain@steele.mgh.harvard.edu

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Online links

DATABASES

The following terms in this article are linked online to:

Cancer.gov: http://www.cancer.gov/cancer_information/
bladder cancer | brain tumours | breast cancer | cervical cancer | colorectal cancer | gastric carcinoma | head and neck tumours | intraocular tumours | lung cancer | mesothelioma | oesophageal cancer | pancreatic cancer | skin cancer

LocusLink: http://www.ncbi.nih.gov/LocusLink/
COX2 | IL-1 | IL-6 | IL-12 | TNF-α | VEGF