Volume 51, Issue 9 / May 2024 / China Laser

Invited Review

Transformation and innovation of photosensitizers

Liu Kaining1,2 , Li Rui1 , Liu Renfa1 ** , Dai Zhifei1*

[1] Department of Biomedical Engineering, School of Future Technology, Peking University, Beijing 100871, China; 2School of Life Sciences, Nankai University, Tianjin 300071, China

AbstractPhotodynamic therapy based on photosensitizers has been identified as a safe treatment for many tumors, skin diseases, vascular diseases and other indications. In recent years, porphyrin photosensitizers and dihydrochlorin photosensitizers have been put into clinical use, and phthalocyanine photosensitizers and polycyclic quinone photosensitizers have been clinically studied. However, photodynamic therapy still faces many problems in clinical transformation, such as limited penetration depth, low solubility, dark toxicity, and high dependence on oxygen concentration. New safe and efficient photosensitizers are urgently needed to be further developed to achieve highly specific minimally invasive treatment. At present, the research and development of new photosensitizers mainly focuses on targeted modification and intelligent nanodrug delivery systems, as well as activatable/responsive photosensitizers, type I photosensitizers that are resistant to hypoxic tumor microenvironment, and photosensitizers that are suitable for the treatment of deep solid tumors. In addition, ultrasound-stimulated sonodynamic therapy has also opened up new ideas for the clinical application of photosensitizers. With the development and transformation of new photosensitizers, more photosensitizer drugs will be used in clinical practice, bringing good news to patients with cancer and other diseases. Keywords: medical optics; photosensitizer; photodynamic therapy; clinical application Chinese Library Classification Number: TQ421.7; R454 Document Code: A

DOI: 10.3788/CJL231365

1 Introduction

Photodynamic therapy (PDT) is a treatment method that uses light to stimulate photosensitizer molecules in the presence of oxygen to generate reactive oxygen species (ROS) that destroy lesions and achieve therapeutic effects. Photodynamic therapy can be traced back to 1900. In 1903, von Tappeiner [1] found that the combination of acridine red and light was lethal to Paramecium, and speculated that the effect was caused by the transfer of energy from the irradiated light to the chemical. With the development of laser technology, the focus of research on photodynamics has shifted from early tumor fluorescence localization diagnosis to clinical disease treatment. In 1993, the Canadian Health Protection Agency approved the photodynamic therapy drug porfibrin sodium (Ptotofrin®) for the treatment of bladder cancer. Subsequently, photodynamic therapy quickly became a research hotspot at home and abroad due to its great potential in the treatment of cancer and some other diseases. At present, photodynamic therapy has become a commonly used treatment method in clinical practice. This method has the advantages of being non-invasive/minimally invasive and having few toxic side effects. It is often used to treat skin diseases such as acne, wet age-related macular degeneration, psoriasis, atherosclerosis, and many superficial lesions. It also plays an important role in the treatment of malignant cancers such as head and neck cancer, lung cancer, bladder cancer, and certain skin cancers [2] . The treatment process of photodynamic therapy [3] is shown in Figure 1 .

The implementation of photodynamic therapy involves three factors: photosensitizer, oxygen and light source. The basic principle of photodynamic therapy is that in the presence of oxygen, photosensitizer produces ROS under the excitation of light, thereby producing a therapeutic effect on the lesion. Most of the unexcited photosensitizer molecules are in the lowest energy ground state (singlet state), with two electrons with opposite spin directions. When the photosensitizer is enriched in the lesion site, the target site is exposed to a specific wave. Under long-term light, after the photosensitizer absorbs photon energy, an electron is excited to a higher energy orbit. This excited state of the photosensitizer molecule is very unstable, and the excited electron tends to transition back to a more stable ground state, while dissipating excess energy in the form of fluorescence and/or heat. When the spin direction of the electron in the excited state is reversed, the photosensitizer molecule jumps from the excited singlet state to the excited triplet state, and then the excited state electron returns to a low energy state, while dissipating energy in the form of radiative transition, producing phosphorescence and triggering type I and type II reactions (Figure 2).

The principle of type I reaction is that the photosensitizer molecules directly interact with organic molecules in the cell microenvironment, obtain hydrogen atoms or electrons to form free radicals, and then the reduced photosensitizer molecules self-oxidize to produce superoxide anion radicals (O2 ·ÿ), which undergo dismutation or single-electron reduction to produce hydrogen peroxide (H2O2), which then undergoes single-electron reduction to become a strong oxidant, hydroxyl radicals (HO·), and trigger a series of reactions, leading to oxidative stress and ultimately destroying cancer cells. The principle of type II reaction is that the triplet photosensitizer molecules transfer energy to molecular oxygen, exciting it into singlet oxygen (1O2). Most of the photosensitizers approved for photodynamic therapy produce singlet oxygen through type II reactions [3-4]. The ROS produced can cause photodamage to proteins, fats and other ÿ molecules in the photosensitive area, leading to apoptosis or necrosis of tumor cells. Different types of cell death depend on the location of the photosensitizer in the cell. Mitochondrial damage can lead to cell apoptosis, cell membrane damage and loss of integrity can lead to cell necrosis, and lysosome or endoplasmic reticulum damage can trigger cell autophagy [5] . Photosensitizers are the key factor in determining the efficacy of photodynamic therapy. Therefore, the development and design

of photosensitizers are still the key to the clinical application of photodynamic therapy.

Received date: 2023- 11- 06; Revised date: 2023- 12- 08; Accepted date: 2023- 12- 12; Online first publication date: 2023- 12- 22

Corresponding author: * zhifei.dai@pku.edu.cn; **liurenfa@pku.edu.cn

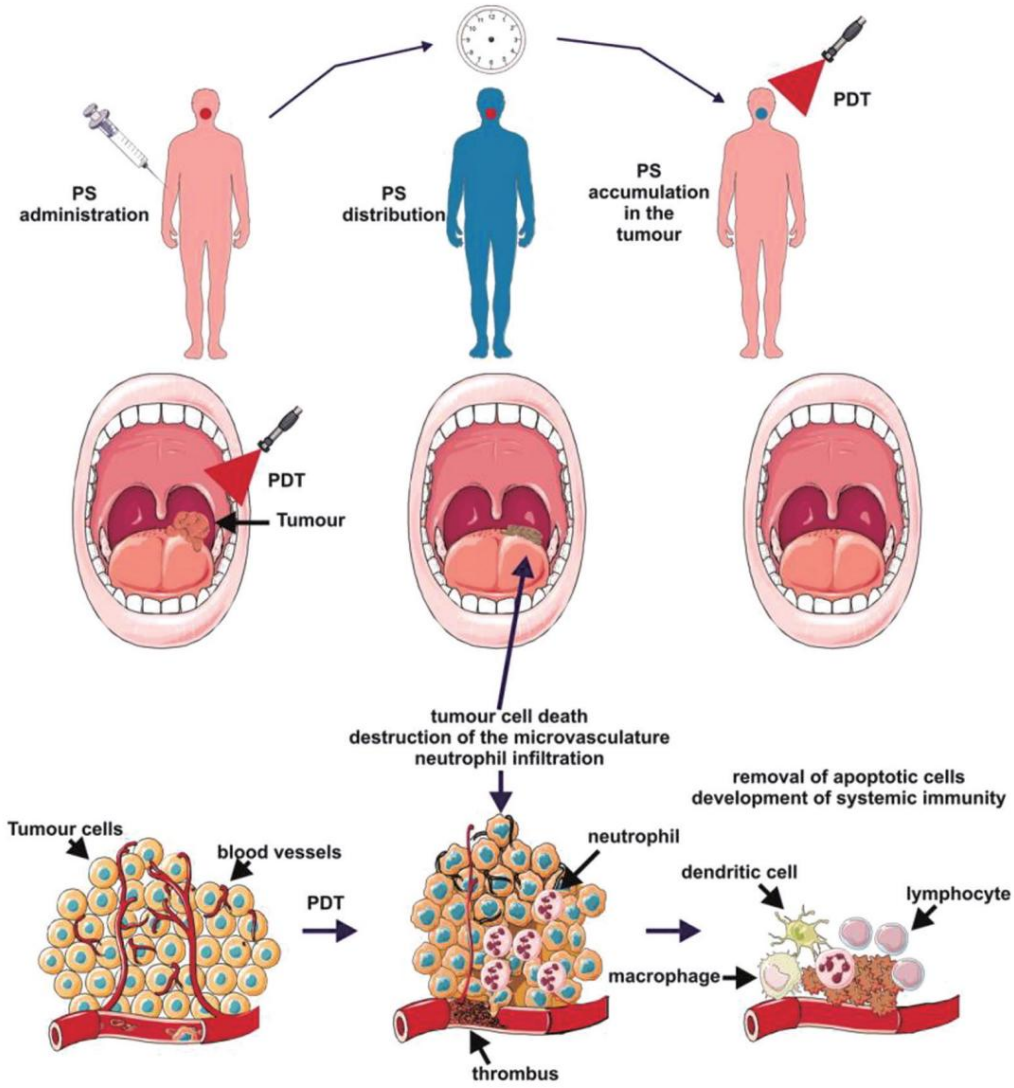

Figure 1 The treatment process of photodynamic therapy [3]

Fig. 1 Treatment process of photodynamic therapy[3]

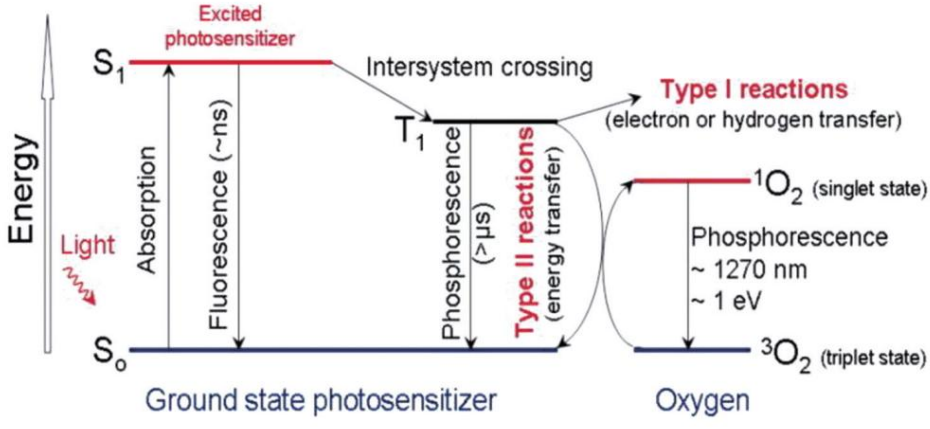

Figure 2 Mechanism of photodynamic reactionÿ3ÿ

Fig. 2 Mechanism of photodynamic reaction[3]

Key points. An ideal photosensitizer should have the following characteristics: 1) a compound with a clear and single composition; 2) a high extinction coefficient between 600 and 800 nm; 3) no toxic side effects and can be cleared from normal tissues quickly; 4) low production cost, easy to store, and low skin phototoxicity.

This article summarizes the photosensitizers that are currently in clinical use or in the clinical trial stage (Table 1), and reviews the latest progress in photosensitizer research in recent years, in order to provide guidance for the development of new, safe and efficient photosensitizers in the future.

Table 1 Photosensitizers used in clinical trials

Table 1 Clinically trial/applied photosensitizers

Name	Wavelength /nm	Administration route	Current status
Hemoporfin	532	ÿ	Approved
Sinoporphyrin sodium	630	ÿ	Clinical phase ÿ
Verteporfin	689	ÿ	Approved
Porfimer sodium	630	ÿ	Approved
Redaporfin	749	ÿ	Clinical phase ÿ
HPPH	665	ÿ	Clinical phase ÿ
Temoporfin	652	ÿ	Approved
Talapophen sodium	664	ÿ	Approved
Chlorin e6	660	ÿ	Clinical phase ÿ
Zinc sulphate	670	ÿ	Clinical phase ÿ
5-FLOOR	635	Topical	Approved
JUST	635	Topical	Approved
MATTER	635	Topical	Approved
Padeliporfin	753	ÿ	Approved
Akalux	690	ÿ	Approved
Rostaporfin	664	ÿ	Clinical phase ÿ
TLD-1433	520	Intravesical	Clinical phase ÿ
Hypericin	590	Topical	Clinical phase ÿ

2 Photosensitizers for clinical use

In clinical practice, precancerous keratinized skin lesions and some non-melanoma skin cancers are often treated with photodynamic therapy. In addition, for several solid tumors including esophageal cancer, lung cancer, and prostate cancer, Photodynamic therapy has been proven to be a feasible treatment strategy and has been proven to be safe and effective. At present, there are relatively few types of photosensitizers used in clinical practice, mostly porphyrin photosensitizers, dihydrochlorin photosensitizers, phthalocyanine photosensitizers and some other photosensitizers, as shown in Figure 3. The categories and characteristics of typical clinically used photosensitizers are summarized in Table 2 .

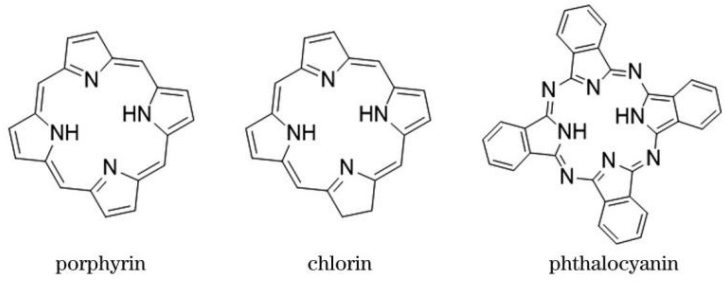

Fig. 3 Structure of photosensitizers commonly used in clinic

2.1 Porphyrin photosensitizers

Porphyrin compounds are the most widely studied photosensitizers. This type of compound consists of four pyrrole rings and side chains connected by methyl bridges. Each porphyrin and its derivatives contain a cyclic tetrapyrrole structure connected by conjugated chains and a large cavity, with 22 P electrons, 18 of which are considered to be conjugated [6] . The raw materials of porphyrin compounds are very abundant (the basic skeleton of chlorophyll is porphyrin), and it is easy to synthesize excellent derivatives. The multidentate coordination effect and its macrocyclic structure characteristics give it many unique physical and chemical properties and functions. Therefore, porphyrin photosensitizers have become a popular scientific research topic The important research direction of the staff [7] .

The porphyrin photosensitizers currently used in clinical practice include hematoporphyrin derivatives, porfimer sodium, verteporfin, hemoporfin, and 5- aminolevulinic acid and its ester derivatives, as shown in Figure 4. Hematoporphyrin derivatives (HpD) are complex mixtures composed of water-soluble porphyrin monomers and oligomers [8-9] . In 1976, Kelly et al. [10] conducted the first clinical trial of HpD on bladder cancer patients. They used HpD to perform photodynamic therapy on 5 patients to delay tumor growth. Subsequently, researchers have used HpD in primary or secondary skin cancer [11] , lung cancer [12-13] , food poisoning, and other diseases.

Table 2 Types and properties of typical clinically used photosensitizers

Table 2 Categories and characteristics of photosensitizers for typical clinical applications

Name	Structure	Indication	Advantage and disadvantage
Porfimer sodium	Porphyrin	Bladder cancerÿ esophageal cancerÿ and lung cancer	Clear structureÿ small side effectsÿ and poor light absorption in the near infrared region
Verteporfin		Choroidal neovascularization	
Hemoporfin		Port wine stain	
5-FLOOR	Porphyrin precursor	Sharp wart	Good safetyÿ non-invasiveÿ and poor effect on deep lesions
JUST		Solar keratosis and basal cell carcinoma	
MATTER		Bladder cancer diagnosis	
Temoporfin	Chlorine	Head and neck cancerÿ prostate cancerÿ and pancreatic cancer	Long maximum absorption wavelength and high molar extinction coefficient
Talapophen sodium		Early lung cancer	
Akalux	Phthalocyanine	Head and neck cancer	High tumor targeting
Padeliporfin	Palladium-coordinated bacterial chlorophyll derivatives	Prostate cancer	Good water solubilityÿ high targeting specificityÿ fast clearance rateÿ high safetyÿ causing hematuria and other adverse reactions

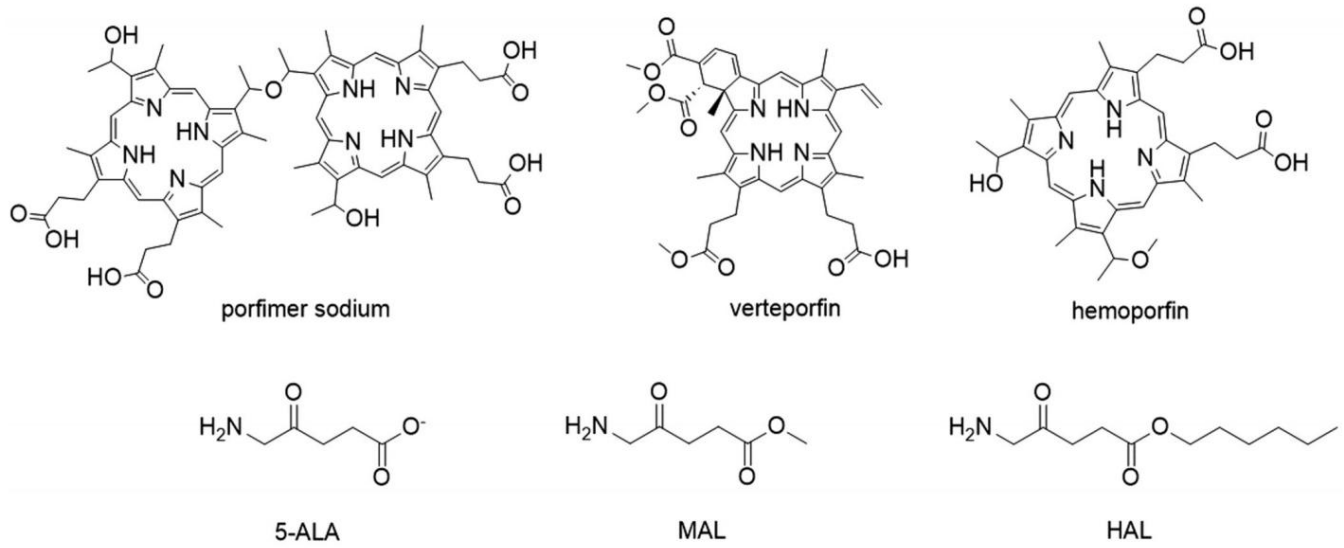

Fig. 4 Structures of porfimer sodium, verteporfin, hemoporfin and 5 - ALA and its ester derivatives

Clinical trials of photodynamic therapy of HpD have been conducted in cancers such as ductal carcinoma and ductal carcinoma [14] . The results showed that this treatment method showed good therapeutic effects in patients with early cancer. Therefore, photodynamic therapy is recommended for the treatment of early cancer patients who cannot undergo surgery due to other complications. The excitation wavelength of HpD is about 405 nm, and the absorption coefficient is 0.126 mL·cm-1 ÿg-1 . Pharmacokinetic studies have shown that the absorption ratio of HpD in tumors and normal tissues is ÿ10, and the retention time in normal tissues is 24~72 h. It is mainly excreted through the liver and gastrointestinal tract. The disadvantages of HpD include unclear components, sun spots after administration, skin photosensitivity and pigmentation when exposed to strong light, and the skin photosensitivity reaction lasts for a long time [15] .

Porfimer sodium, also known as photosensitive element II, is the product of HpD purification. In the early research of HpD, due to technical limitations, researchers have not been clear about the specific components of HpD.

Nowadays, double hematoporphyrin ether (DHE) is the main active ingredient of HpD, and its mass accounts for 45%~50% of the total mass of the mixture [16-17] . The mass fraction of active ingredients such as DHE in photosensitin II is above 80%. In 1993, porphyrin sodium was officially produced by Canadian QLT Company. At present, porphyrin sodium has been approved for the treatment of bladder cancer, esophageal cancer, and lung cancer, and has become the most commonly used photosensitizer in photodynamic therapy of non-cutaneous solid tumors. At the current clinical dosage, porfimer sodium has many advantages, such as good tolerance by patients, good water solubility, and no need for solubilizing excipients. However, it still has some shortcomings, such as: 1) Porphynom sodium is a mixture composed of multiple components, and the role of each component in photodynamic therapy is unclear; 2) Porphynom sodium is at 630 nm. The absorbance is low and the absorption at 400~500 nm is significant, resulting in long-term skin photosensitivity. Patients need to avoid light for 4~6 weeks after surgery; 3) Low selectivity for diseased tissues; 4) Effective treatment of all Need agent

5) The apparent elimination half-life is long, with an average of 21.5 daysÿ18-19 ÿ „

Verteporfin is the first photosensitizer approved for the treatment of choroidal neovascularization (CNV) in clinical practice. It has been used to treat age-related macular degeneration (AMD), degenerative myopia, choroidal neovascularization, and histoplasmosis. The main target of verteporfin-based photodynamic therapy for CNV is considered to be vascular occlusion secondary to CNV [20] . Verteporfin is used in the form of a liposome preparation, which is preferentially taken up by cells that overexpress low-density lipoprotein receptors (such as neovascular endothelial cells). When excited by a 689 nm laser, verteporfin undergoes a photosensitization reaction to produce singlet oxygen and free radicals, causing damage to the vascular endothelium and destroying capillaries. The maximum plasma concentration of verteporfin occurs at the end of intravenous infusion of the drug, and the elimination half-life is about 6 hours. Its rapid uptake and clearance increases the possibility of selective damage to neovascular endothelial cells, while reducing the effects on the retinal pigment epithelium (RPE) and retina, and reducing the risk of systemic photosensitivity [21] . The adverse reactions of verteporfin PDT are RPE damage and vascular occlusion effects, which can be alleviated by adjusting the treatment parameters. In recent years, the emergence of vascular endothelial growth factor inhibitors has greatly limited the application of verteporfin PDT, but verteporfin PDT can still be used to treat diseases such as central serous chorioretinopathy (CSCR), choroidal hemangioma and polypoidal choroidal vasculopathy (PCV) [22] .

The chemical component of hemoporfin is hematoporphyrin monomethyl ether (HMME), which is a new type of photosensitizer with a single composition and stable properties. It is often used clinically to treat port-wine stains (PWS). PWS manifests as a low-flow vascular malformation of dermal capillaries and post-capillary venules. During photodynamic therapy for PWS, HMME is rapidly absorbed by vascular endothelial cells after intravenous administration and is rarely absorbed by dermal extravascular stroma and epidermal cells. After irradiation with 532 nm laser, the diseased vascular endothelial cells are destroyed by the singlet oxygen produced, thereby selectively destroying the abnormal capillary network [23] . HMME has the advantages of rapid distribution in the body, short clearance time, short light avoidance period, fast healing, and light pigmentation [24] , making it suitable for the treatment of all

It is particularly suitable for treating large lesions (diameter greater than 5 cm) of various types of port-wine

stains. Aminolevulinic acid (5- ALA) is an endogenous non-protein amino acid and is the starting compound for the synthesis of heme in mammals and chlorophyll in plants. It is metabolized in vivo to produce protoporphyrin IX (PpIX) [25] . PpIX produces strong red fluorescence when excited by a laser of about 400 nm. When excited by red and blue light, it undergoes a photodynamic reaction to produce singlet oxygen, which can be used in photodynamic diagnosis and treatment [26] . 5-ALA is administered topically. After penetrating the skin and entering the cells, 5-ALA interacts with heme in the biosynthesis of heme and selectively converts more into PpIX in malignant tissues. ALA-photodynamic therapy has been used to treat basal cell carcinoma, actinic keratosis, acne, psoriasis, viral warts, port-wine stains, and some other skin diseases [27] . In order to increase the dose of ALA and PpIX in thickened skin lesions and achieve better therapeutic effects, researchers have developed two ALA ester derivatives for photodynamic diagnosis and treatment: ALA methyl ester (MAL) and ALA hexyl ester (HAL). ALA methyl ester and ALA hexyl ester have a higher absorption rate in the skin and mucous membranes. After entering the cells, they are first converted to demethyl ester or dehexyl ester.

5- ALA, and then further converted to PpIXÿ25ÿ . ALA methyl ester has been approved for clinical use in Europe for basal cell carcinoma (BCC) of the face and scalp that is not suitable for other treatments, as well as thin or non-hyperkeratotic and non-pigmented actinic keratosis (AK)ÿ28ÿ . ALA hexyl ester is clinically used for the diagnosis of bladder cancer.

2.2 Chlorin-type photosensitizers

Chlorin, that is, two hydrogen atoms are

combined at the 3 and 4 positions of one of the four pyrrole nuclei of porphyrin, so that a double bond between carbon atoms is converted into a single bond. It is one of the stable degradation products of chlorophyll a. Chlorins and their derivatives have attracted widespread attention due to their strong photosensitization reaction ability, high targeting specificity and low toxicity and side effects. However, poor water solubility and low in vivo clearance are the disadvantages of this type of photosensitizer. Currently, the dihydrochlorin photosensitizers used clinically include temoporfin (mTHPC) and talaporfin sodium (NPe6),

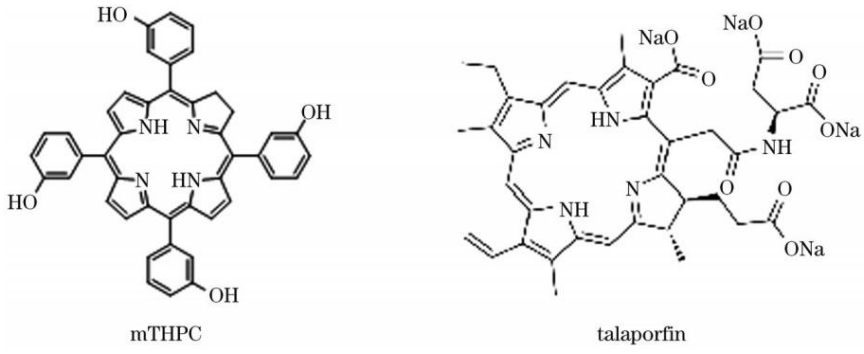

Fig. 5 Structures of mTHPC (left) and talaporfin (right)

Temoporfin (mTHPC) can be prepared as a chemically pure compound, and its concentration in tumor tissue is 14 times higher than that in normal tissue. The maximum absorption wavelength of mTHPC is 652 nm, and the photosensitization reaction is highly efficient (fluorescence quantum yield is about 20%), so only a small dosage, a short treatment time and a low light dose are required.

It can achieve the photodynamic response required for treatment. Compared with photofrin II, it has higher phototoxicity to tumors and shorter duration of skin phototoxicity. All skin photosensitivity phenomena occurred in cases exposed to sunlight within the first week after administration [29] . mTHPC is clinically used to treat head and neck squamous cell carcinoma.

Talaporfin sodium (NPe6) is a chlorophyll a degradation product derivative. It is clinically used for patients with early lung cancer who cannot receive radical treatment such as surgery or who need to preserve lung function but cannot receive other treatments. The maximum absorption wavelength of talaporfin sodium is 664 nm, and it is highly water-soluble and has a short half-life. The molecule contains 4 carboxyl groups and has a large number of anionic charges, which allows it to be cleared from the body more quickly. Talaporfin sodium is mainly bound to albumin in the body and is mainly eliminated from the body through bile excretion. 48 hours after bile duct cannulation, the excretion rates of radiolabeled talaporfin sodium in bile, urine and feces were 84.6%, 0.5% and 1.0% of the administered dose, respectively. In vivo pharmacokinetic studies of human and rat metabolism have shown that talaporfin sodium is almost not involved in in vivo metabolism and is highly safe [30] .

2.3 Phthalocyanine

photosensitizers Phthalocyanine (PCs) is an aromatic heterocycle composed of four nitrogen atoms connected to an isoindole ring. Phthalocyanine photosensitizers have many advantages in photodynamic therapy applications due to their high maximum absorption wavelength (>670 nm) and high extinction coefficient (>1×105 mol·L-1 cm-1). In addition to strong absorption in the phototherapy window, phthalocyanines show low or no absorption in the wavelength range of higher sunlight intensity (400~600 nm), thereby reducing the degree of skin photosensitivity caused by sunlight. In addition, the chemical structure of phthalocyanine compounds can be easily modified by introducing central metals and axial, peripheral and non-peripheral substituents. These changes give phthalocyanines easily adjustable physical and chemical properties, pharmacokinetics and biodistribution properties [31] . Currently, clinically used phthalocyanine photosensitizers include Photosens® and Akalux, as shown in Figure 6 .

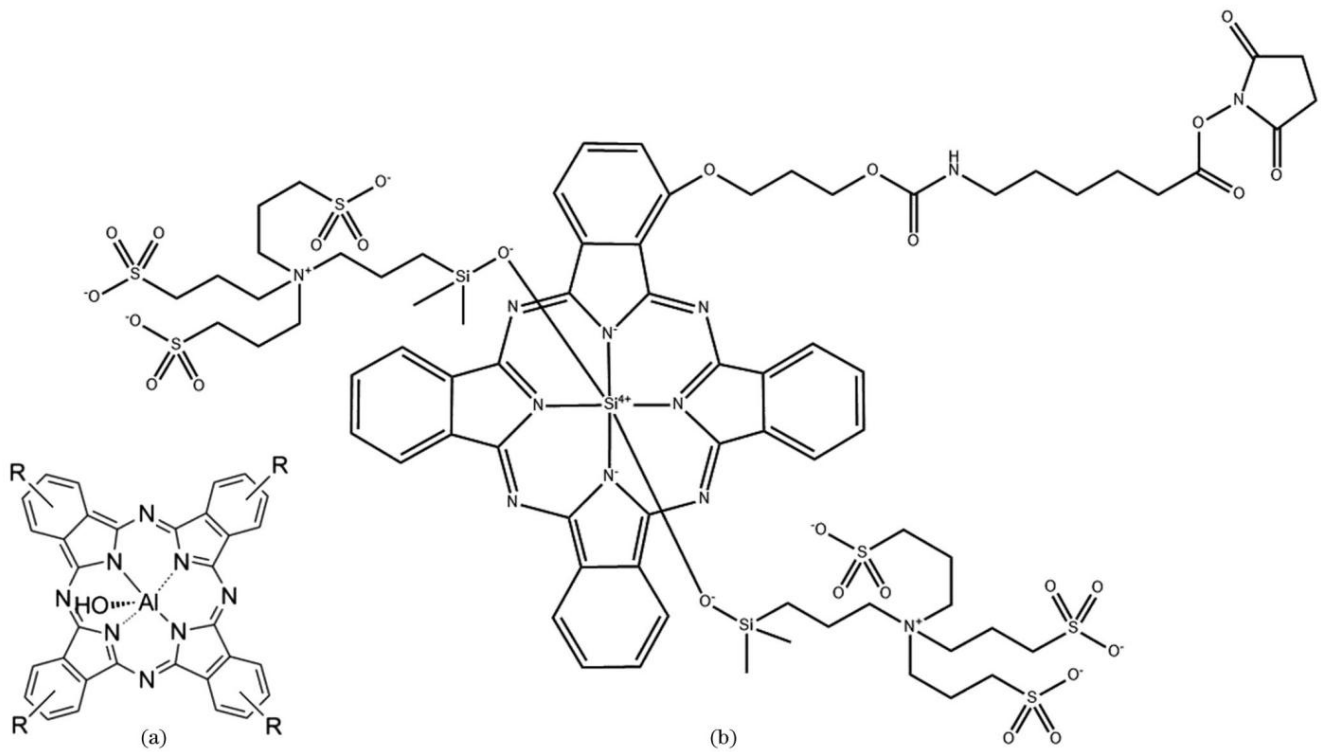

Fig.6 Structures of Photosens® (a) and IRDye700DX (b)

Photosens® is a distilled aqueous solution of sulfonated aluminum sodium phthalocyanine (AlPcS) with a maximum absorption at 675 nm. Developed and commercialized by NIOPIC Moscow Research and Production Association, Photosens® is highly effective against a wide range of cancers of different tissue types and stages, such as squamous cell skin cancer, breast cancer, oropharyngeal cancer, lung cancer, eyelid-related tumors, bladder cancer, and cervical cancer. It can also be used to treat severe purulent wounds, trophic ulcers, and some other non-malignant diseases. Photosens® is administered by intravenous injection in clinical use, with a dosage of 0.5-2.0 mg/kg. However, skin photosensitivity is a serious side effect of this drug, and patients should avoid light for 6-10 weeks after treatment [32] .

Akalux is a combination of cetuximab and IRDye700DX (abbreviated as IR700) can target epidermal growth factor receptor

Photoimmunotherapy is an emerging tumor-targeted phototherapy that combines photodynamic therapy and antibody therapy. It can not only achieve high tumor specificity through antibody-mediated targeted delivery, but also induce tumor necrosis and immunogenic cell death, leading to local and systemic innate immune responses and acquired immune responses. Akalux can be used for photoimmunotherapy of tumors: cetuximab is used to provide targeting, and IR700 is used to kill tumors, as shown in Figure 7. In September 2020, Japan approved Akalux for the treatment of head and neck malignant tumors, and an international Phase III clinical trial for locally recurrent head and neck squamous cell carcinoma is underway [33] . 2.4 Other photosensitizer drugs In recent years,

derivatives of chlorophyll and

bacterial chlorophyll have also attracted attention. Paliporfin is a water-soluble, palladium-coordinated

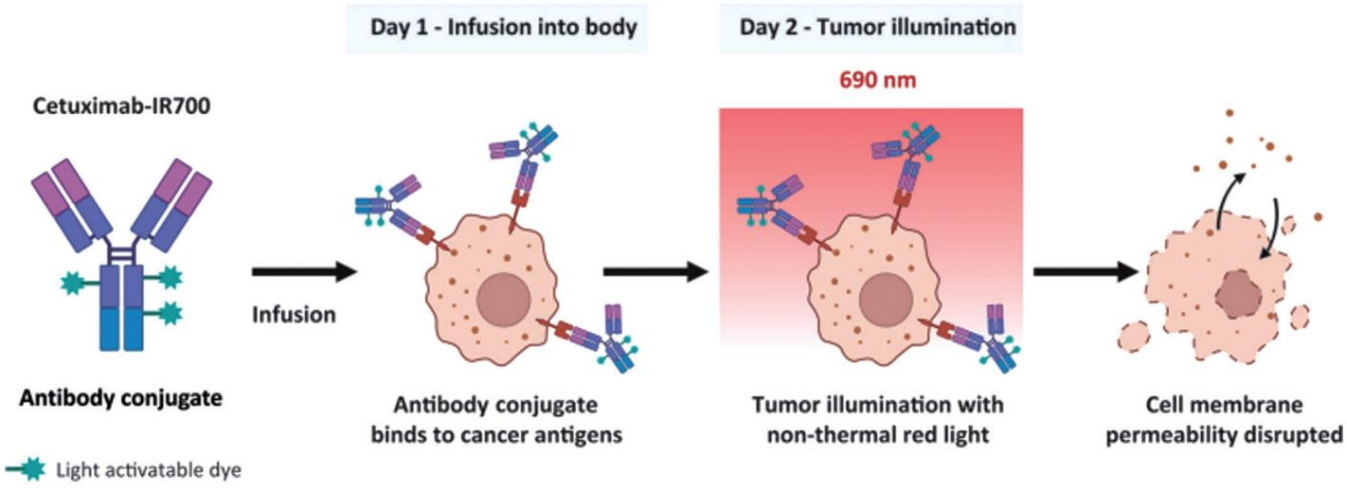

Figure 7 Tumor-targeting antibody conjugated to a photosensitizer. After in vivo administration, the tumor is irradiated with non-thermal red light (690 nm) to achieve anticancer activity mediated by biophysical processes that disrupt cell membrane integrity [33]

Fig. 7 Combination of tumor-targeted antibody and photosensitizer. After *in vivo* administration, irradiate the tumor with non-thermal red light (690 nm), resulting in anticancer activity mediated by biophysical processes that disrupt cell membrane integrity[33]

The bacterial chlorophyll derivative of paliporfin has been approved for marketing in Europe for the treatment of prostate cancer. As a photosensitizer for vascular targeted photodynamic therapy [34], paliporfin directly targets and accumulates in prostate cancer cells through the blood circulation, and is excited by a 753 nm laser in the cancer cells to produce a large amount of ROS, inducing tumor cell apoptosis or necrosis. This photodynamic reaction leads to vascular occlusion at the lesion site, promoting tumor ablation. Preclinical pharmacokinetic studies have shown that paliporfin is only present in the blood circulation after intravenous administration, and is confined to the vascular system even at high doses, and can be rapidly cleared by the liver and kidney systems [35] . The rapid clearance of paliporfin in tissues may be related to the introduced taurine group. Taurine is a ÿ-amino acid in the cell fluid, widely distributed in the liver of mammals, and participates in the liver's detoxification process. During the detoxification process, taurine binds to different molecules in the liver to increase the water solubility of the drug. This promotes the clearance of drugs by the liver .ÿ36ÿ Clinical research results show that vascular targeted photodynamic therapy with paliporfin does not cause problems such as skin photosensitivity and is highly safe.

3 Photosensitizers in clinical trials

As people's research on photodynamic therapy continues to deepen, more and more photosensitizers have been developed by researchers. At present, many photosensitizers have entered the clinical trial stage, such as phthalocyanine forsine, polycyclic quinone hypericin, metal coordination rhodopsin derivative ropeporfin, porphyrin sodium porphyrin, dihydrochlorin derivative pyrochlorophyllin a hexyl ether, ruthenium pyridine complex TLD-1433, bacteriochlorin derivative redaporfin, etc., as shown in Figure 8. The categories and characteristics of typical photosensitizers in the clinical trial stage are summarized in Table 3 .

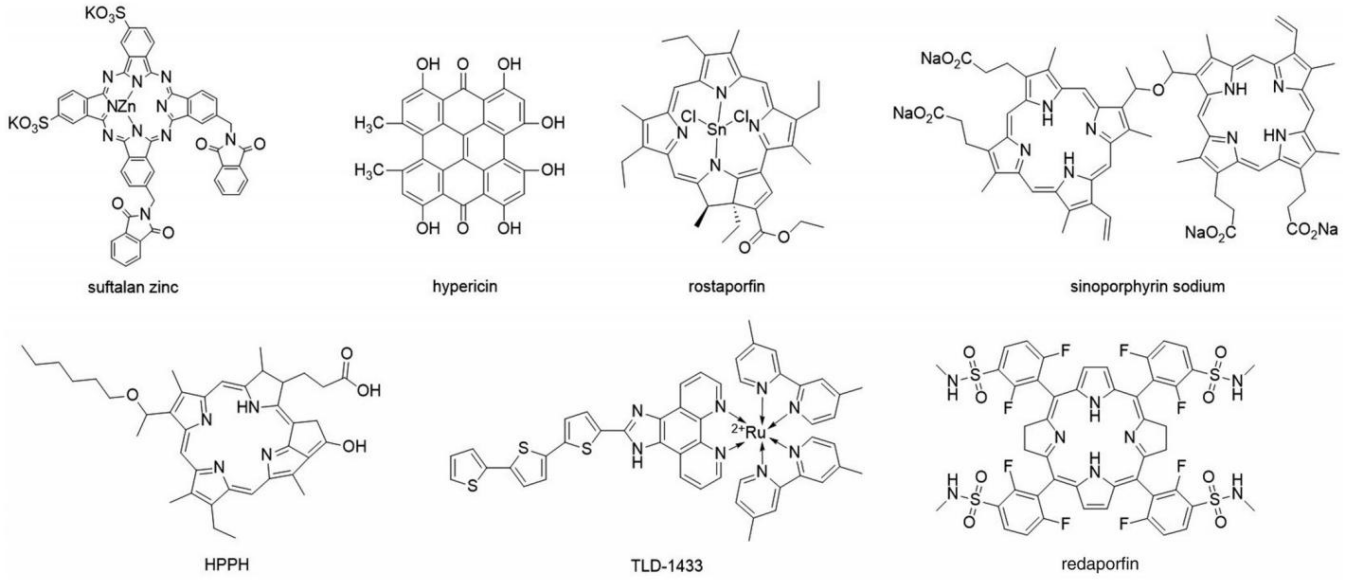

Fig. 8 Structures of suftalan zinc, hypericin, rostaporfin, sinoporphyrin sodium, HPPH, TLD-1433, and redaporfin

Table 3 Types and properties of typical photosensitizers in clinical trials

Table 3 Categories and characteristics of typical photosensitizers in clinical trials

Name	Structure	Indication	Advantage and disadvantage
Zinc sulphate	Phthalocyanine	Esophagus cancer	Amphiphilic propertiesÿ high singlet oxygen yieldÿcausing adverse reactions such as abnormal liver and kidney function
Hypericin	Viscous cycloquinone	Cutaneous T-cell lymphoma	Poor solubility and high singlet oxygen yield
Rostaporfin	Tin-coordinated anthapurpurin derivatives	Metastatic breast cancer and Kaposi's sarcoma	Long maximum absorption wavelengthÿ having skin phototoxicity
Sinoporphyrin sodium	Porphyrin	Esophagus cancer	Clear active ingredientÿ good water solubilityÿ and small toxic side effects
HPPH	Chlorine	Oral squamous cell carcinoma	Long maximum absorption wavelengthÿsmall toxic side effectsÿ short time of avoiding lightÿ causing adverse reactions such as retrosternal pain

Forsythene is a mixture of four isomers of di(sulfonate potassium) -diphthalimidomethyl phthalocyanine zinc (ZnPcS2P2), developed by Chen Naisheng and others from Fuzhou University [31] . The maximum absorption wavelength of forsythene is 670 nm. The drug is amphiphilic, which is conducive to its transport in the circulatory system and its uptake by tumor cells; at the same time, its singlet oxygen quantum yield is high, and only one -tenth of the dose of porphyrin sodium is required to achieve the same therapeutic effect [37] . Forsythene was approved by the former State Food and Drug Administration (now the State Administration for Market Regulation) for Phase I clinical trials in 2008, and is currently undergoing Phase II clinical trials for esophageal cancer. Hypericin is a secondary metabolite mainly found in plants of the genus

Hypericum. It belongs to the polycyclic quinone photosensitizer class and has great potential for treating diseases. The maximum absorption band of hypericin is at 590 nm, and it has high singlet oxygen and ROS quantum yields. As a highly efficient natural photosensitizer, hypericin has shown great potential in photodynamic therapy and photodynamic diagnosis, especially in the treatment of cancer and bacterial infections. However, the poor solubility of hypericin greatly limits its pharmacological effects. Therefore, researchers have made some structural modifications to hypericin and developed various hypericin drug delivery systems to improve the solubility of hypericin. Recently, a clinical trial showed that hypericin-photodynamic therapy has good efficacy and safety for fungal cutaneous T-cell lymphoma, and the study has been advanced to the clinical phase III trial stage [38] .

Ropeporfin is a tin-coordinated rhodamine derivative that is complexed with tin with two , chlorine ligands. It can produce a stronger photosensitization reaction than rhodamine without a complexed metal. The maximum absorption band of Ropeporfin is at 664 nm. It is insoluble in water and needs to be made into an isotonic lipid emulsion suitable for intravenous infusion for clinical application. Ropeporfin is currently undergoing a Phase III clinical study for metastatic breast cancer. The results showed that within a follow-up period of at least 6 months after photodynamic therapy, the complete response rate of breast cancer patients was 92%, the partial response rate was 8%, and lesions smaller than 0.5 cm were completely relieved [39] . Sodium porphyrin is a porphyrin photosensitizer with high yield and easy purification that was screened out after a systematic

study of photosensin. Compared with photosensin II

In comparison, the active ingredient of sodium chloranthate is clear, with a mass fraction of up to 98%, good water solubility, low dark toxicity and strong phototoxicity. The effective dose is only one-tenth of that of photosensitive hormone II, and the light avoidance time after treatment is expected to be shortened to 3-7 days. The maximum absorption wavelength of sodium chloranthate is 630 nm, and it is administered by intravenous injection. The indications are advanced solid tumors, advanced esophageal cancer, and primary esophageal cancer with residual local lesions after radical chemoradiotherapy or radiotherapy or local recurrence after complete remission. At present, the clinical phase I study of sodium chloranthate has been completed, and phase II and phase III clinical trials

are underway [40] . Pyrochlorophyllin a-hexyl ether (HPPH) is a Class 1.1 new drug photosensitizer under development by Hisun Pharmaceuticals and is a dihydrochlorin derivative. The maximum absorption wavelength of HPPH is at 665 nm, and it has the advantages of a single structure, low dark toxicity, and short light avoidance time. The research on HPPH in the treatment of oral squamous cell carcinoma has been advanced to clinical phase II [41] . The ruthenium pyridine complex TLD-1433 is the first ruthenium-based photosensitizer to enter clinical trials. It is currently undergoing a Phase II clinical trial for the treatment of non-muscle invasive bladder cancer via intravesical instillation. Redaporfin is a new type of bacteriochlorin derivative photosensitizer under development. It has good photostability and can achieve a large charge transfer interaction with oxygen molecules. The maximum absorption wavelength of redaporfin is at 749 nm. It is clinically administered by intravenous injection. It is currently undergoing a Phase II clinical trial for the treatment of head and neck tumors [42] .

4 Innovation of photosensitizers

In recent years, new safe and efficient photosensitizers combined with other technologies have been continuously developed. With the rapid development of nanotechnology, nano drug delivery carriers are increasingly being used in photodynamic therapy. At the same time, new photosensitizers with precise targeting functions for lesions, activatable and responsive photosensitizers, type I photosensitizers that are resistant to hypoxic tumor microenvironments, and photosensitizers adapted to the treatment of deep solid tumors are being continuously developed in order to achieve artificially controllable, precise, and efficient photodynamic therapy. At the same time, the combined application of photodynamic therapy with other treatment methods has received more and more attention. In addition, sonodynamic therapy, as a derivative application of photosensitizers, has been widely used because of its greater penetration depth.

4.1 Application of nanotechnology in photodynamic therapy Traditional photosensitizers have low water solubility and tissue/cell specificity, which reduces the efficiency of photodynamic therapy. In recent years, nanotechnology has developed rapidly, and the combination of photosensitizer-dependent photodynamic therapy and nanotechnology has become a mainstream trend. Encapsulating photosensitizer drugs into nanoparticles can not only improve the solubility and stability of photosensitizers [43] , but also achieve passive targeting of tumors through the high permeability and long retention (EPR) effect. Before/during photodynamic therapy, the use of nano-oxygen-carrying platforms to supplement molecular oxygen in situ in the tumor microenvironment can effectively reduce the inhibitory effect of hypoxia on photodynamic therapy [44-45] . The use of polymer nanoparticles, such as liposomes, micelles, carbon nanomaterials and gold nanoparticles, can deliver more photosensitizer molecules to the tumor area in a targeted manner and prevent the degradation of photosensitizers before reaching the target tumor tissue [46-47].

Liposomes are a relatively mature system for targeted delivery of photosensitizers to tumor tissues. Based on the EPR effect, the loaded photosensitizer drugs can be delivered to tumor tissues. The first photosensitizer that uses liposomes as a drug delivery carrier is HpD. Studies have shown that using liposomes to deliver HpD for photodynamic therapy can achieve better therapeutic effects. Visudyne, a liposome formulation of verteporfin, has been approved by the FDA (U.S. Food and Drug Administration) as a drug for the treatment of wet AMD. In addition to liposome delivery systems, lipoprotein delivery systems have also been widely studied. Since there are a large number of low-density lipoprotein receptors on the surface of tumor cells, it is also beneficial to bind photosensitizers to low-density lipoproteins. Several studies have shown that compared with the photosensitizer itself, non-covalent bonding of photosensitizers to low-density lipoproteins before administration will increase the efficiency of photodynamic therapy [48-49]. The use of smart nanodelivery systems to achieve more precise targeted photodynamic therapy has attracted attention. Wang Yiguang's team [50] based on pH ultrasensitive Sensing (UPS) nanotechnology platform, a series of nanophotosensitizer drugs (ANPS) libraries with different pH transition points have been established, and the intracellular early endosome-late endosome-lysosome pathway is divided into 10 based on subtle pH differences. stage, the photosensitizer chlorin e6 is precisely targeted and delivered to the endosomes at specific stages. The results show that compared with late endosome- and lysosome-targeted nanoparticles, ROS produced by early endosome-targeted nanoparticles can effectively activate phospholipase C signaling, thereby efficiently inducing Gasdermin-E-mediated cellular pyrolysis. Death. The use of this nanotechnology platform increases the anti-tumor effect in vitro and in vivo by 40 times and 20 times respectively, achieving safe and efficient tumor treatment on a variety of subcutaneous/orthotopic tumor models. 4.2 New Targeted Photosensitizers In addition to nanodelivery systems, research on targeted photosensitizers also shows broad prospects. Surface modification of photosensitizers combined with active targeting moieties such as antibodies, peptides, and aptamers [51] can significantly improve the targeting specificity of photosensitizer drugs and reduce toxic and side effects on non-targeted normal tissues and organs of the body.

Carbonic anhydrase IX (CAIX) is considered a marker of poor survival and distant metastasis in invasive breast cancer. Its highly restricted expression in normal tissues and specific overexpression in tumor sites make it a potential therapeutic target. Kim's team [52] designed an acetazolamide (AZ)-coupled BODIPY photosensitizer (AZ-BPS). AZ-BPS uses the high affinity of AZ to CAIX to achieve targeting of invasive cancer cells that overexpress CAIX, successfully combining the advantages of anti-angiogenic therapy and photodynamic therapy, and reducing the impact of hypoxia on photodynamic therapy (as shown in Figure 9). Compared with BPS (BODIPY photosensitizer), AZ-BPS enhances the in vivo efficacy of xenograft mouse tumor regeneration models and also achieves good therapeutic effects on clinical samples of breast cancer patients.

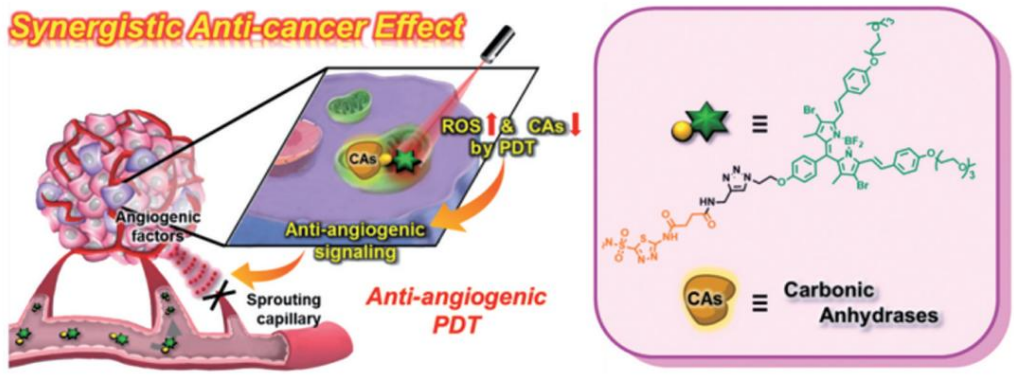

Figure 9 Schematic diagram of the synergistic anticancer effect of AZ-BPS targeting CAIXÿ52ÿ

Fig. 9 Schematic diagram of synergistic anticancer effects of AZ-BPS targeting CAIX[52]

Biotin receptors are overexpressed on the surface of most tumor cells. Peng Xiaojun's research group introduced biotin as a target group into the photosensitizer molecule and synthesized a photosensitizer that can target biotin receptor-positive tumors. ENBS-B (as shown in Figure 10). Benefiting from the targeting ability of the biotin ligand, the cellular uptake rate of ENBS-B in cancer cells is 87 times higher than that in normal cells [53] . The experimental results show that even in an oxygen-deficient environment (the volume fraction of O2 is 2%), ENBS-B can be uptaken by the type I reaction mechanism. A large amount of O2-· is generated , and part of the O2-· is converted into highly biologically toxic OH· through a cascade reaction mediated by superoxide dismutase (SOD) . These free radicals can synergistically destroy the lysosomes in the cells, thereby triggering tumor cell apoptosis and showing a strong hypoxic photodynamic therapy effect. 4.3 Activatable responsive photosensitizers In recent years, some researchers have focused on the design of activatable responsive new photosensitizers to achieve more precise and controllable photodynamic response.

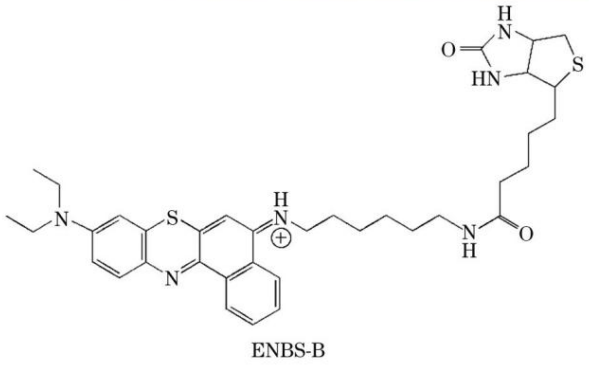

Fig. 10 Structure of ENBS-B

Professor Zhang Xi's teamÿ54ÿ designed and synthesized a near-infrared photothermal 5,10,15,20- tetrakis(4- N-methylpyridyl)porphyrin (TMPyP) with conversion properties . This compound will be reduced to porphyrin by reducing facultative anaerobic bacteria in hypoxic environment, but still behaves as a photosensitizer in aerobic environment. Based on this bacteria-responsive porphyrin, the team achieved adaptive photodynamic/photothermal antibacterial (as shown in Figure 11), which showed excellent antibacterial effects in different environments. 4.4 Type I photosensitizers resistant to hypoxic tumor microenvironment

Most existing photodynamic therapies are based on type II photosensitization reactions, which are highly dependent on O2 levels and involve a large amount of O2 consumption. However, hypoxia (ÿO2 ÿ <7 ÿmol/L) is a major feature of the microenvironment of solid tumors. Photodynamic therapy-mediated oxygen consumption and microvascular damage further aggravate hypoxia in the tumor site, ultimately leading to poor treatment efficacy.

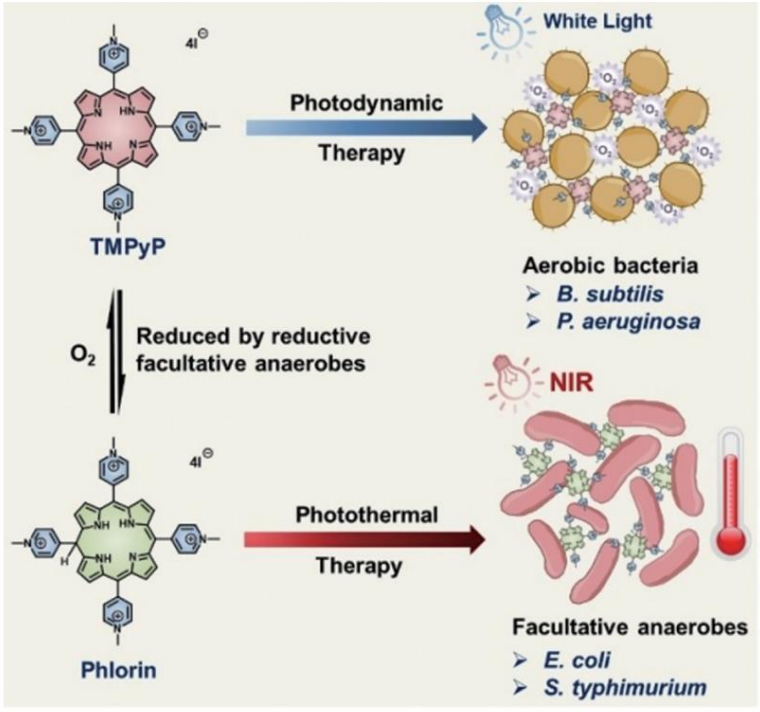

Figure 11 Schematic diagram of adaptive photodynamic and photothermal therapy of bacteria in response to the porphyrin TMPyPÿ54ÿ

Fig. 11 Schematic diagram of adaptive photodynamic and photothermal therapy of TMPyP in response to bacteria[54]

Photosensitizers that undergo a type I reaction when the electrons of the excited-state photosensitizer return to the ground state are called type I photosensitizers. Under light excitation, the excited-state electrons of type I photosensitizers can be transferred to oxygen molecules to produce superoxide anions, which undergo a dismutation reaction with the participation of superoxide dismutase to release oxygen, thus providing an efficient solution for overcoming tumor hypoxia. Huang Jiandong's team [4, 55] designed and synthesized a multifunctional silicon phthalocyanine derivative (PcAF) containing a perphenazine group. PcAF can form a stable and uniform NanoPcAF through a self-assembly process in an aqueous solution (as shown in Figure 12). NanoPcAF exhibits efficient type I photosensitization ability and can produce a large number of superoxide anion radicals. In an oxygen-deficient environment, NanoPcAF produces 3.4 times more superoxide anion radicals than the photosensitizer methylene blue (MB). In preclinical model studies, NanoPcAF showed good tumor accumulation after systemic administration, and no obvious toxicity.

4.5 Photosensitizers suitable for the treatment of deep-seated solid tumors. Near-infrared light excitation can achieve greater penetration depth, but traditional near-infrared photosensitization methods have problems such as low conversion efficiency and difficulty in molecular design. In view of this, Deng Renren's team [56] developed a simple lanthanide-triplet sensitization method, which achieves high-performance near-infrared photosensitization by coupling organic photosensitizers to lanthanide nanoparticles (as shown in the figure) shown in 13). This method can efficiently generate ROS under ultra-low near-infrared radiation, and has high application value in fields such as tumors and infectious diseases. Compared with traditional photodynamic therapy, the photosensitizer used in this photodynamic therapy can treat disease tissue depth and treatment efficiency are significantly improved (more than 40 clinical and scientific research photosensitizers were compared). For some high-efficiency photosensitizers that absorb short wavelengths and ha

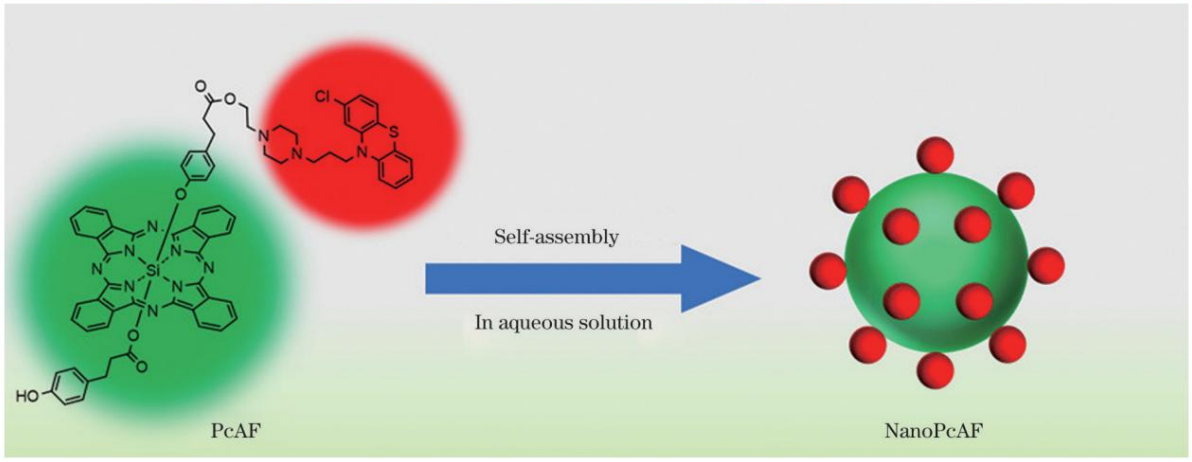

Figure 12 Chemical structure of PcAF and its self-assembly to form NanoPcAFÿ55ÿ

Fig. 12 Chemical structure of PcAF and its self-assembly to form NanoPcAF[55]

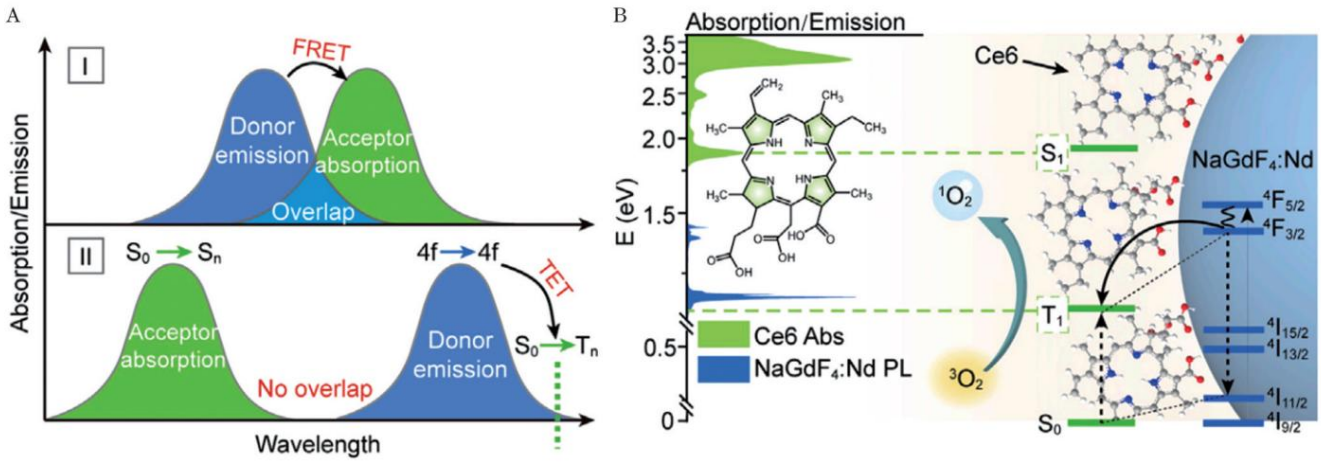

Figure 13 Schematic diagram of lanthanide-triplet energy transferÿ56ÿ

Fig. 13 Schematic illustration of lanthanide-triplet energy transfer[56] (Spectral diagrams in image A showing: (I) Förster resonance energy transfer (FRET) through overlapped donor emission and acceptor absorption; (II) direct lanthanide-triplet energy transfer (TET) from a 4f excited state of a lanthanide ion and a triplet state of an organic phosphor. Schematic illustration B displays the proposed direct triplet sensitization process in a NaGdF4ÿ Nd-Ce6 hybrid system. Note that the absorption (Abs) of Ce6 and the photoluminescence (PL) of NaGdF4ÿ Nd show no spectral overlap)

In order to solve the problem that the ROS yield of photosensitizers absorbed by the system is relatively low, researchers have proposed a two-photon excitation photodynamic strategy. Photosensitizers with short-wavelength absorption absorb two near-infrared photons (about twice the absorption wavelength of the photosensitizer) and are excited to produce ROS, which provides a possibility for the treatment of deep lesions. Li Junbai's team [57] found that emo (Emo) is a promising two-photon excitation photosensitizer with a large two-photon absorption cross-section (TPAC: 380.9 GM) and a high singlet oxygen (1 O2) quantum yield (31.9%). When co-assembled with human serum albumin (HSA), the formed Emo/HSA nanoparticles (E/H NPs) have a huge TPAC (4.02×107 GM) and ideal 1 O2 generation ability, showing excellent two-photon excitation-photodynamic therapy (TPE-PDT) effect, as shown in Figure 14 . In vivo experiments showed that E/H NPs showed a longer retention time at the tumor site and ablated the tumor at a very low dose (0.2 mg/kg) under 800 nm femtosecond pulse laser excitation. Karges et al. [58-59] designed a photosensitizer based on a ruthenium and polypyridine complex and verified its efficacy in two-dimensional monolayer cells, three-dimensional cell spheroids, and subcutaneous tumor models.

TPE-PDT effect. One hour after the photosensitizer was injected into the mouse, 800 nm light (50 mW, 1 kHz, 35 fs pulse width, 5 s/mm) was used for photodynamic therapy of subcutaneous tumors with a volume of 80 mm3. The results showed that 800 nm light had a good inhibitory effect on tumor growth, even better than the single-photon photodynamic therapy effect of 500 nm light (60 min, 10.0 mW/cm2 , 36 J/cm2). 4.6 Combination therapy of

photosensitizers with other drugs With the maturity

and promotion of photodynamic therapy, in order to achieve better therapeutic effects and lower toxic side effects, the combination of photodynamic therapy with other existing therapies such as chemotherapy or immunotherapy has begun to attract attention. Ossendorp's team [60] studied the combined use of bremachlorin-based photodynamic therapy and a therapeutic synthetic long peptide vaccine (SLP). The results showed that the combined therapy could effectively eradicate tumors. In addition, the combined treatment of primary tumors led to the elimination of distant secondary tumors, and all cured mice were protected from tumor recurrence. This indicates that the combined therapy successfully induced a systemic anti-tumor immune response in the

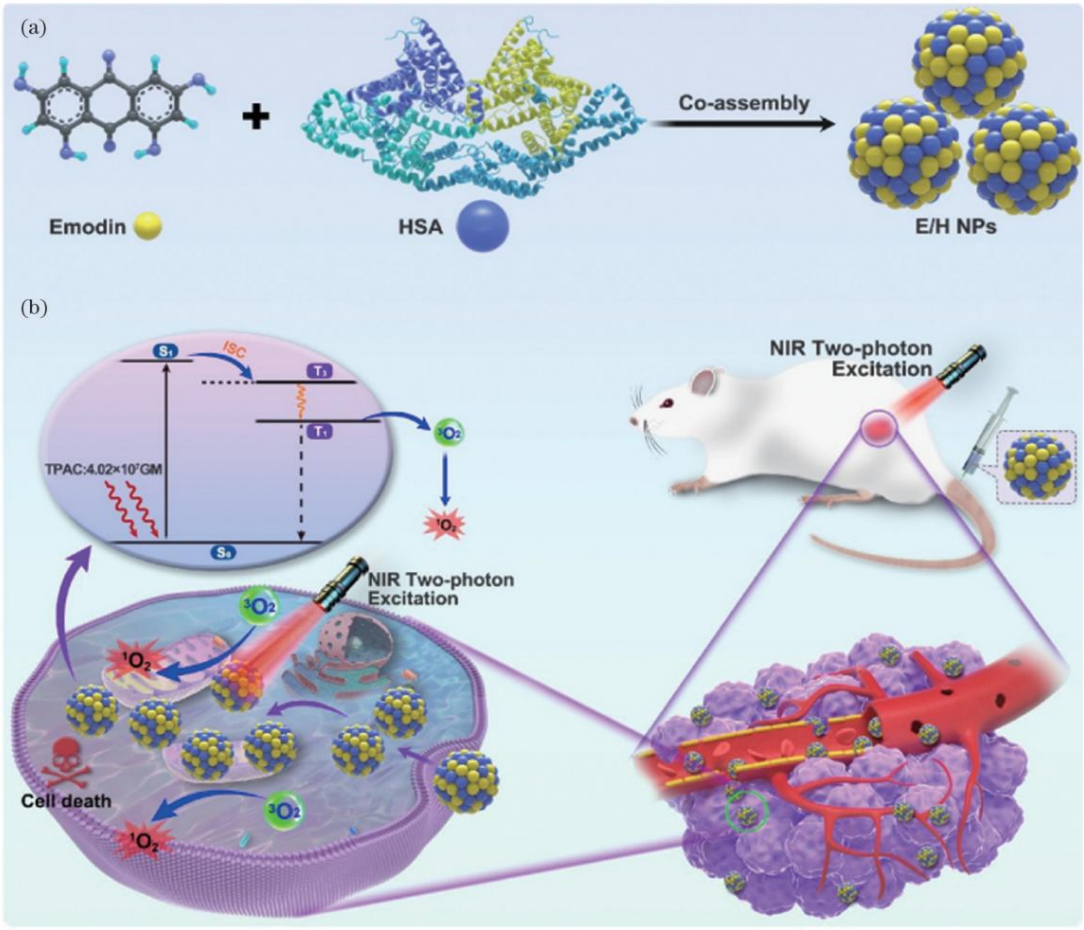

Figure 14 Schematic diagram of the synergistic assembly of rheumatoid arthritis nanoparticles for efficient two-photon excitation photodynamic anticancer effects [57] . (a) Preparation of Emo/HSA nanoparticles using the synergistic assembly strategy; (b) Emo/HSA nanoparticle-mediated efficient two-photon excitation photodynamic anticancer

Fig. 14 Schematic illustrations of co-assembly of emodin nano-drugs for efficient anti-cancer TPE-PDT[57] . (a) Preparation of Emo/HSA NPs by co-assembly strategy; (b) Emo/HSA NPs mediated efficient anti-cancer TPE-PDT

The team [61] combined porphyrin sodium photodynamic therapy with proton radiation therapy for the treatment of malignant pleural mesothelioma. Combination therapy showed excellent local control and overall survival rates and was well tolerated by patients, significantly reducing radiation therapy toxicity. Some other research groups have also confirmed that photodynamic therapy can improve the efficacy of chemical drug therapy and ionizing radiation therapy [62-63] . At the same time, the combined application of photodynamic therapy, gene therapy, siRNA therapy, etc. has also attracted the attention of researchers [64-65] 4.7 Derived applications of photosensitizers: sonodynamic therapy

Sonodynamic therapy (SDT) is a new non-invasive treatment mode derived from photodynamic therapy, involving the combination of low-intensity ultrasound and sonosensitizers. It has received widespread attention in recent years. The principle of sonodynamic therapy is similar to that of traditional photodynamic therapy: in the presence of oxygen, ultrasound activates sonosensitizers to produce ROS to treat the lesions (as shown in Figure 15). Currently, most commonly used sonosensitizers are photosensitizers in nature. Some organic molecules (porphyrin derivatives, Bengal rose red, cyanine dyes, natural products), inorganic nanomaterials (TiO2, ZnO, Fe3O4, MnWOx and black phosphorus) and their hybrid materials have been used in sonodynamic therapy for cancer research [66] . Unlike light, ultrasound has a strong tissue penetration ability, with a penetration depth of more than 10 cm in soft tissue (the maximum penetration depth of light into tissue is only on the millimeter scale), so sonodynamic therapy can have The main limitation of photodynamic therapy has been effectively overcome by using sonodynamic therapy [67] . Since the late 1980s, sonodynamic therapy has become a promising cancer

treatment modality. Several photosensitizers that have been approved for clinical use are also undergoing clinical trials related to sonodynamic therapy, including sodium chrysoporphyrin and 5- ALA. The ultrasound frequency required for clinical use of sodium chrysoporphyrin is 1 MHz, 30% duty cycle, 15 min treatment time, indications for atherosclerosis, peripheral arterial disease, cardiovascular disease, and is currently undergoing phase II clinical trials. The ultrasound frequency required for clinical use of 5-ALA is 1 MHz, the sound intensity is 2.65 W/cm2 , the treatment time is 16 min, and the indication is high-grade glioma. It is currently undergoing phase I clinical trials. There are also many studies that combine sonodynamic

therapy with other therapies to achieve better therapeutic effects. For example, Yue et al. [68] designed a tumor treatment regimen based on sonosensitizer-enhanced, non-invasive sonodynamic therapy combined with anti-PD-L1 checkpoint blockade immunotherapy (1 MHz, 1.5 W/cm2 , 50% duty cycle) (as shown in Figure 16). Hemoporfin is used as a sonosensitizer and imiquimod (R837) is used as a Toll-like receptor agonist. Both are loaded onto FDA-approved liposomes to prepare nanoparticles HMME/R837@Lip. The researchers used 4T1 and CT26 mouse models to

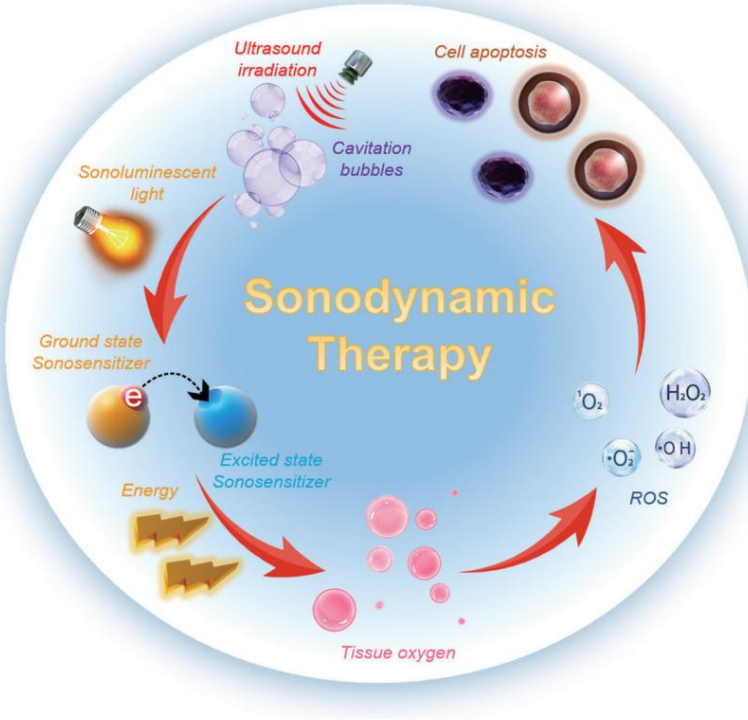

Figure 15 Schematic diagram of sonodynamic therapy [67]

Fig. 15 Schematic diagram of sonodynamic therapy[67]

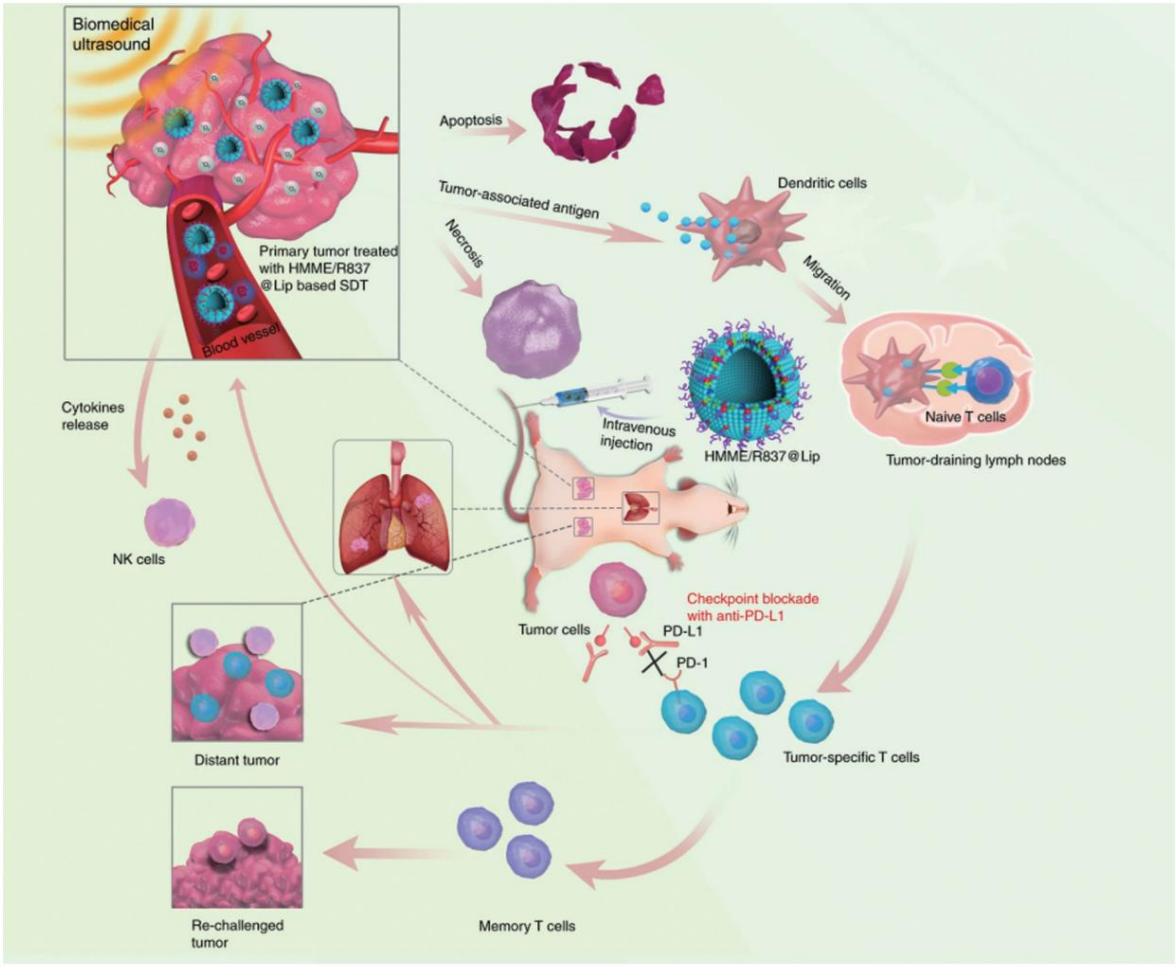

Figure 16 Design principle of synergistic treatment of nanosonosensitizer SDT and immunotherapyÿ68ÿ

Fig. 16 Design principle of synergistic therapy of nano sonosensitizer SDT and immunotherapy[68]

The delayed tumor retention of HMME/R837@Lip was demonstrated

High tumor accumulation phenomenon. HMME-mediated sonodynamic therapy achieves

Primary tumors were treated, and anti-PD-L1 immunotherapy achieved lung metastasis suppression

system, thereby enhancing the overall therapeutic effect.

Most reported sonosensitizers are also photosensitizers, so treatment

Skin photosensitivity is still a problem that needs to be solved in sonodynamic therapy.

Although sonodynamic therapy solves the

Low light penetration problem, but the actual treatment efficiency is still affected by the lack of tumor

Oxygen barriers, oxygen-carrying materials, in situ in the tumor microenvironment (TME)

Strategies to increase local molecular oxygen levels in tumors, such as generating molecular oxygen, are being developed.

Being explored. Safer and more efficient, with higher ROS generation capability

In particular, sonosensitizers that can only be activated in the tumor microenvironment are still

In addition, combining sonodynamic therapy with the original

Combinations of drugs developed for non-cancer diseases may have a role in cancer treatment

In order to achieve better clinical

Clinical treatment effect, sonodynamic therapy still has many factors that need to be further studied

Step adjustment and optimization[66].

5 Conclusion

Since the phenomenon of photosensitization was first recognized in 1900,

Through the efforts of generations of researchers, people have understood the photodynamic effect.

The principle of photodynamic therapy has been recognized in the treatment of skin diseases, malignant tumors and other diseases.

With the discovery of new theories and the development of new technologies,

People have a better understanding of the components and structures of photosensitizer molecules and are gradually able to design

The synthesis of a novel molecule with a clear chemical composition, high ROS quantum yield, and molar extinction

High coefficient, low skin photosensitivity, short circulation time in the body, specific for

New photosensitizer for blood vessels or other tissues at the site of disease.

Research on phototherapy dosimetry enables accurate quantification of photodynamic therapy in clinical practice

The dosage can be adjusted in real time according to the individual differences of patients.

Optimization is possible.

After the relationship between quantity and quantity, photodynamic therapy will be more widely clinically

Applications[69-70].

At present, porphyrin photosensitizers are the most widely used category.

Chlorophene photosensitizers, condensed ring quinone photosensitizers, phthalocyanine photosensitizers, etc. or

Clinical applications have been achieved or clinical trials are in progress.

The research on photosensitizers is still progressing, such as: constructing liposomes, liposomes

New nano drug delivery system for better photosensitizer delivery

Effect; Develop modified target groups or activatable responsive photosensitizers to achieve

More precise and controllable photodynamic therapy; development of hypoxia-resistant tumor microenvironment

Type I photosensitizer reduces the oxygen concentration in the tumor site caused by photodynamic therapy

Dependence on; developed lanthanide-triplet sensitization method, proposed two-photon excitation

Photodynamic strategy, etc., has expanded the application of photodynamic therapy in the treatment of deep solid tumors.

At the same time, photodynamic therapy is closely related to other existing treatment methods such as

Combined application of chemotherapy, immunotherapy and photosensitizer derivatives

Use - Sonodynamic therapy, in the treatment of deep solid tumors and other diseases

We are constantly exploring and moving forward. I believe that with the continuous exploration of scientific researchers

In the future, there will be more photosensitizer drugs with high efficiency and low toxicity.

Dedicated to the cause of human life and health.

References

[1] by Tappeiner H. On the effect of fluorescent substances on enzymes and toxins[J]. Reports of the German Chemical Society, 1903, 36(3): 3035-3038.

[2] Chen J, Keltner L, Christophersen J, et al. New technology for deep light distribution in tissue for phototherapy[J]. Cancer Journal, 2002, 8(2): 154-163.

[3] Agostinis P, Berg K, Cengel K A, et al. Photodynamic therapy of cancer: an update[J]. CA: a Cancer Journal for Clinicians, 2011, 61 (4): 250-281.

[4] Chen W L, Wang Z H, Tian M Y, et al. Integration of TADF photosensitizer as “electron pump” and BSA as “electron reservoir” for boosting type I photodynamic therapy[J]. Journal of the American Chemical Society, 2023, 145(14): 8130-8140.

[5] Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy: mechanisms, photosensitizers and combinations[J]. Biomedicine & Pharmacotherapy, 2018, 106: 1098-1107.

[6] Rajora M A, Lou J W H, Zheng G. Advancing porphyrin’s biomedical utility via supramolecular chemistry[J]. Chemical Society Reviews, 2017, 46(21): 6433-6469.

[7] Zhang Li, Jiang Jianqin. Research progress of porphyrin photosensitizers[J]. Yunnan Chemical Industry, 2018, 45 (11): 1-6.
Zhang L, Jiang J Q. Research progress of porphyrin photosensitizers [J]. Yunnan Chemical Technology, 2018, 45(11): 1-6.

[8] Lipson R L, Baldes E J, Olsen A M. The use of a derivative of hematoporhyrin in tumor detection[J]. Journal of the National Cancer Institute, 1961, 26: 1-11.

[9] Lipson R L, Baldes E J, Olsen A M. Hematoporphyrin derivative: a new aid for endoscopic detection of malignant disease[J]. The Journal of Thoracic and Cardiovascular Surgery, 1961, 42(5): 623-629.

[10] Kelly J F, Snell M E. Hematoporphyrin derivative: a possible aid in the diagnosis and therapy of carcinoma of the bladder[J]. The Journal of Urology, 1976, 115(2): 150-151.

[11] Dougherty T J, Kaufman J E, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumors[J]. Cancer Research, 1978, 38(8): 2628-2635.

[12] Balchum O J, Doiron D R, Huth G C. Photoradiation therapy of endobronchial lung cancers employing the photodynamic action of hematoporphyrin derivative[J]. Lasers in Surgery and Medicine, 1984, 4(1): 13-30.

[13] Hayata Y, Kato H, Konaka C, et al. Hematoporphyrin derivative and laser photoradiation in the treatment of lung cancer[J]. Chest, 1982, 81(3): 269-277.

[14] McCaughan J S, Jr, Hicks W, Laufman L, et al. Palliation of esophageal malignancy with photoradiation therapy[J]. Cancer, 1984, 54(12): 2905-2910.

[15] Han Fangli, Wu Biqiong, Xiong Jun, et al. Effects of hematoporphyrin derivatives (HPD) on laser diagnosis and treatment of malignant tumors. Application in tumors[J]. Applied Laser, 1996, 16(2): 93-94.
Han F L, Wu B Q, Xiong J, et al. Application of hematoporphyrin derivatives (HPD) in laser diagnosis and treatment of malignant tumors[J]. Applied Laser, 1996, 16(2): 93-94.

[16] Dougherty T J, Potter W R, Weishaupt K R. The structure of the active component of hematoporphyrin derivative[J]. Progress in Clinical and Biological Research, 1984, 170: 301-314.

[17] Dougherty T J. Hematoporphyrin as a photosensitizer of tumors[J]. Photochemistry and Photobiology, 1983, 38(3): 377-379.

[18] Dougherty T J, Cooper M T, Mang T S. Cutaneous phototoxic occurrences in patients receiving Photofrin®[J]. Lasers in Surgery and Medicine, 1990, 10(5): 485-488.

[19] Dolmans D E J G J, Fukumura D, Jain R K. Photodynamic therapy for cancer[J]. Nature Reviews Cancer, 2003, 3: 380-387.

[20] Renno R Z, Miller J W. Photosensitizer delivery for photodynamic therapy of choroidal neovascularization[J]. Advanced Drug Delivery Reviews, 2001, 52(1): 63-78.

[21] Keam S J, Scott L J, Curran M P. Verteporfin: a review of its use in the management of subfoveal choroidal neovascularisation[J].

Drugs, 2003, 63(22): 2521-2554.

[22] Battaglia Parodi M, La Spina C, Berchicci L, et al. Photosensitizers and photodynamic therapy: verteporfin[J]. Developments in Ophthalmology, 2016, 55: 330-336.

[23] Yu Li, Li Xiaoyuan. Research progress on the second-generation photosensitizer hematoporphyrin monomethyl ether and its clinical application [J]. Biomedical Engineering and Clinical, 2005, 9(6): 365-368.

Yu L, Li X Y. Advances in the second generation of photosensitizer hematoporphyrin monomethyl ether and its clinical applications[J]. Biomedical Engineering and Clinical Medicine, 2005, 9(6): 365-368.

[24] Gu Ying, Li Junheng, Wang Kai, et al. Hemomorphine methyl ether for photodynamic therapy of port-wine stain A preliminary clinical study on nevus[J]. Chinese Journal of Laser Medicine, 1996, 5(4): 17-20.

Gu Y, Li J H, Wang K, et al. Preliminary clinical observation of HMME in PDT for PWS[J]. Chinese Journal of Laser Medicine & Surgery, 1996, 5(4): 17-20.

[25] Jiang Jie, Zou Jian, Zhu Xingmei, et al. 5-aminolevulinic acid and its esters in photodynamic therapy Research progress of derivatives[J]. Acta Laser Biologica Sinica, 2019, 28(4): 289-295.

Jiang J, Zou J, Chu ESM, et al. Research progress of 5-aminolevulinic acid and its esters in photodynamic diagnosis and therapy[J]. Acta Laser Biology Sinica, 2019, 28(4): 289-295.

[26] Stringasci M D, Ciol H, Romano R A, et al. MAL-associated methyl nicotinate for topical PDT improvement[J]. Journal of Photochemistry and Photobiology B, 2020, 213: 112071.

[27] Fan L L, Yin R, Lan T, et al. Photodynamic therapy for rosacea in Chinese patients[J]. Photodiagnosis and Photodynamic Therapy, 2018, 24: 82-87.

[28] Morton C A. Methyl aminolevulinate (Metvix) photodynamic therapy-practical pearls[J]. The Journal of Dermatological Treatment, 2003, 14(Suppl 3): 23-26.

[29] Grosjean P, Savary J F, Wagnières G, et al. Tetra(m-hydroxyphenyl)chlorin clinical photodynamic therapy of early bronchial and oesophageal cancers[J]. Lasers in Medical Science, 1996, 11(4): 227-235.

[30] Wang S, Bromley E, Xu L, et al. Talaporfin sodium[J]. Expert Opinion on Pharmacotherapy, 2010, 11(1): 133-140.

[31] Liu M, Li C H. Recent advances in activatable organic photosensitizers for specific photodynamic therapy[J]. ChemPlusChem, 2020, 85(5): 948-957.

[32] Jiang Z, Shao J W, Yang T T, et al. Pharmaceutical development, composition and quantitative analysis of phthalocyanine as the photosensitizer for cancer photodynamic therapy[J]. Journal of Pharmaceutical and Biomedical Analysis, 2014, 87: 98-104.

[33] Cognetti D M, Johnson J M, Curry J M, et al. Phase 1/2a, open-label, multicenter study of RM-1929 photoimmunotherapy in patients with locoregional, recurrent head and neck squamous cell carcinoma[J]. Head & Neck, 2021, 43(12): 3875-3887.

[34] Chen Ruijie, Niu Yanhui, Chen Tianlong, et al. Narrow-band photohemotherapy in vascular targeted photodynamic therapy Hybrid registration algorithm for tube images[J]. Laser and Optoelectronics Progress, 2022, 59(6): 0617020.

Chen R J, Niu Y H, Chen T L, et al. Hybrid registration method of narrow-band blood vessel image for vascular targeted photodynamic therapy[J]. Laser & Optoelectronics Progress, 2022, 59(6): 0617020.

[35] Azzouzi A R, Barret E, Bennet J, et al. TOOKAD® Soluble focal therapy: pooled analysis of three phase II studies assessing the minimally invasive ablation of localized prostate cancer[J]. World Journal of Urology, 2015, 33(7): 945-953.

[36] Min Xiangyan, Cao Ning, Yan Yijia, et al. Research progress of the new photodynamic drug paliporfin[J]. Progress in Science, 2019, 43(3): 231-237.

Min X Y, Cao N, Yan Y J, et al. Research progress in new photodynamic therapy with padeliporfin[J]. Progress in Pharmaceutical Sciences, 2019, 43(3): 231-237.

[37] Zheng X, Cui X G, Yu H D, et al. Development of a quantitative method for four photocyanine isomers using differential ion mobility and tandem mass spectrometry and its application in a preliminary pharmacokinetics investigation[J]. Journal of Chromatography A, 2018, 1577: 109-119.

[38] Wu J J, Zhang J, Xia C Y, et al. Hypericin: a natural anthraquinone as promising therapeutic agent[J]. Phytomedicine, 2023, 111: 154654.

[39] Karges J. Clinical development of metal complexes as photosensitizers for photodynamic therapy of cancer[J]. Angewandte Chemie (International Ed. in English), 2022, 61(5): e202112236.

[40] Zhu Bing, Li Shanxin, Zhang Hong, et al. Research progress on the anti-tumor effect of sodium chloroporphyrin[J]. Journal of Second Military Medical University, 2018, 39(11): 1259-1264.

Zhu B, Li S X, Zhang H, et al. Advance on anti-tumor activities of sinoporphyrin sodium[J]. Academic Journal of Second Military Medical University, 2018, 39(11): 1259-1264.

[41] Nava H R, Allamaneni S S, Dougherty T J, et al. Photodynamic therapy (PDT) using HPPH for the treatment of precancerous lesions associated with Barrett's esophagus[J]. Lasers in Surgery and Medicine, 2011, 43(7): 705-712.

[42] Arnaut L G, Pereira M M, Dÿbrowski J M, et al. Photodynamic therapy efficacy enhanced by dynamics: the role of charge transfer and photostability in the selection of photosensitizers[J]. Chemistry, 2014, 20(18): 5346-5357.

[43] Yang H Y, Liu R F, Xu Y X, et al. Photosensitizer nanoparticles boost photodynamic therapy for pancreatic cancer treatment[J]. Nano-Micro Letters, 2021, 13(1): 35.

[44] Li X S, Kwon N, Guo T, et al. Innovative strategies for hypoxic-tumor photodynamic therapy[J]. Angewandte Chemie (International Ed. in English), 2018, 57(36): 11522-11531.

[45] Xu Y X, Liu R F, Yang H Y, et al. Enhancing photodynamic therapy efficacy against cancer metastasis by ultrasound-mediated oxygen microbubble destruction to boost tumor-targeted delivery of oxygen and renal-clearable photosensitizer micelles[J]. ACS Applied Materials & Interfaces, 2022, 14(22): 25197-25208.

[46] Hong E J, Choi D G, Shim M S. Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials [J]. Acta Pharmaceutica Sinica B, 2016, 6(4): 297-307.

[47] Li X S, Lovell J F, Yoon J, et al. Clinical development and potential of photothermal and photodynamic therapies for cancer[J]. Nature Reviews Clinical Oncology, 2020, 17: 657-674.

[48] Mazière J C, Morlière P, Santus R. The role of the low density lipoprotein receptor pathway in the delivery of lipophilic photosensitizers in the photodynamic therapy of tumours[J]. Journal of Photochemistry and Photobiology B, 1991, 8(4): 351-360.

[49] Luisa Andreazza N, Vevert-Bizet C, Bourg-Heckly G, et al. Berberine as a photosensitizing agent for antitumoral photodynamic therapy: insights into its association to low density lipoproteins[J]. International Journal of Pharmaceutics, 2016, 510(1): 240-249.

[50] Chen B L, Yan Y, Yang Y, et al. A pyroptosis nanotuner for cancer therapy[J]. Nature Nanotechnology, 2022, 17: 788-798.

[51] Paszko E, Ehrhardt C, Senge M O, et al. Nanodrug applications in photodynamic therapy[J]. Photodiagnosis and Photodynamic Therapy, 2011, 8(1): 14-29.

[52] Jung H S, Han J Y, Shi H, et al. Overcoming the limits of hypoxia in photodynamic therapy: a carbonic anhydrase IX-targeted approach[J]. Journal of the American Chemical Society, 2017, 139 (22): 7595-7602.

[53] Yang Yuxin, Zhao Xueze, Fan Jiangli, et al. Improving the targeting of photosensitizers in photodynamic therapy Research progress of [J]. CIESC Journal, 2021, 72(1): 1-13.

Yang Y X, Zhao X Z, Fan J L, et al. Research progress on improving the tumor-targeting of photosensitizers in photodynamic therapy[J]. CIESC Journal, 2021, 72(1): 1-13.

[54] Hu H, Wang H, Yang Y C, et al. A bacteria-responsive porphyrin for adaptable photodynamic/photothermal therapy[J]. Angewandte Chemie (International Ed. in English), 2022, 61(23): e202200799.

[55] Zhao Y Y, Zhang L, Chen Z X, et al. Nanostructured phthalocyanine assemblies with efficient synergistic effect of type I photoreaction and photothermal action to overcome tumor hypoxia in photodynamic therapy[J]. Journal of the American Chemical Society, 2021, 143(34): 13980-13989.

[56] Zheng B Z, Zhong D N, Xie T T, et al. Near-infrared photosensitization via direct triplet energy transfer from lanthanide nanoparticles[J]. Chem, 2021, 7(6): 1615-1625.

[57] Liu YL, Zhao J, Xu X, et al. Emodin-based nanoarchitectonics with giant two-photon absorption for enhanced photodynamic therapy[J]. Angewandte Chemie, 2023, 135(33): e202308019.

[58] Karges J, Kuang S, Maschietto F, et al. Rationally designed ruthenium complexes for 1- and 2-photon photodynamic therapy[J]. Nature Communications, 2020, 11: 3262.

[59] Wang Shaowei, Lei Ming. Research progress of two-photon excited photodynamic therapy[J]. China Laser, 2022, 49(15): 1507101.
Wang S W, Lei M. Recent advances in two-photon excited photodynamic therapy[J]. Chinese Journal of Lasers, 2022, 49(15): 1507101.

[60] Kleinovink JW, van Driel PB, Snoeks TJ, et al. Combination of photodynamic therapy and specific immunotherapy efficiently eradicates established tumors[J]. Clinical Cancer Research, 2016, 22(6): 1459-1468.

[61] Rice S R, Li Y R, Busch T M, et al. A novel prospective study assessing the combination of photodynamic therapy and proton radiation therapy: safety and outcomes when treating malignant pleural mesothelioma[J]. Photochemistry and Photobiology, 2019, 95(1): 411-418.

[62] Pigula M, Huang H C, Mallidi S, et al. Size-dependent tumor response to photodynamic therapy and irinotecan monotherapies revealed by longitudinal ultrasound monitoring in an orthotopic pancreatic cancer model[J]. Photochemistry and Photobiology, 2019, 95(1): 378-386.

[63] Broekgaarden M, Rizvi I, Bulin AL, et al. Neoadjuvant photodynamic therapy augments immediate and prolonged oxaliplatin efficacy in metastatic pancreatic cancer organoids[J]. Oncotarget, 2018, 9(16): 13009-13022.

[64] Zhang M J, Weng Y H, Cao Z Y, et al. ROS-activatable siRNA-engineered polyplex for NIR-triggered synergistic cancer treatment [J]. ACS Applied Materials & Interfaces, 2020, 12(29): 32289-32300.

[65] Zhao R R, Liang X L, Zhao B, et al. Ultrasound assisted gene and photodynamic synergistic therapy with multifunctional FOXA1-siRNA loaded porphyrin microbubbles for enhancing therapeutic efficacy for breast cancer[J]. Biomaterials, 2018, 173: 58-70.

[66] Son S, Kim J H, Wang X W, et al. Multifunctional sonosensitizers in sonodynamic cancer therapy[J]. Chemical Society Reviews, 2020, 49(11): 3244-3261.

[67] Ouyang J, Tang Z M, Farokhzad N, et al. Ultrasound mediated therapy: recent progress and challenges in nanoscience[J]. Nano Today, 2020, 35: 100949.

[68] Yue W W, Chen L, Yu L D, et al. Checkpoint blockade and nanosonosensitizer-augmented noninvasive sonodynamic therapy combination reduces tumour growth and metastases in mice[J]. Nature Communications, 2019, 10: 2025.

[69] Zhu T C. Dosimetry in pleural photodynamic therapy[J]. Journal of the National Comprehensive Cancer Network: JNCCN, 2012, 10 (Suppl 2): S60-S64.

[70] LI Buhong, XIE Shusen, WILSON Brian C. Study on dosimetry of photodynamic therapy
Progress in Biochemistry and Biophysics, 2009, 36(6): 676-683.
Li B H, Xie S S, Wilson B C. Advances in photodynamic therapy dosimetry[J]. Progress in Biochemistry and Biophysics, 2009, 36 (6): 676-683.

Translation and Innovation of Photosensitizers

Liu Kaining1,2 , Li Rui1 Liu Renfa1**, Dai Zhifei1*

[1] *Department of Biomedical Engineering, College of Future Technology, Peking University, Beijing* 100871, *China;*

[2] *College of Life Sciences, Nankai University, Tianjin* 300071, *China*

Abstract

Significance Photodynamic therapy (PDT) is a novel treatment for superficial skin diseases and tumors. The basic treatment involves administering a photosensitizing agent through intravenous injection or other methods, and then stimulating the lesion with a specific wavelength of light. This photodynamic reaction, facilitated by the photosensitizing agent, effectively cures the lesion. PDT uses the photodynamic effect for diagnosing and treating diseases. Its mechanism is based on a photosensitization reaction accompanied by biological effects that includes the participation of oxygen molecules. This process involves irradiating a laser of a specific wavelength to excite a photosensitizer that has been absorbed by tissues, causing it to enter an excited state. Then the photosensitizer in the excited state transfers energy to the surrounding oxygen, resulting in the generation of highly active singlet oxygen. This singlet oxygen undergoes an oxidative reaction with adjacent biological macromolecules, inducing cytotoxicity, and ultimately, causing cell damage and death. Over the past 20 years, PDT has emerged and developed as a new treatment technology for diseases such as esophageal cancer, lung cancer, condyloma acuminatum, acne, and nevus.

Compared to traditional tumor therapies such as surgery, chemotherapy, and radiotherapy, PDT offers unique and irreplaceable advantages. It is non-resistant, allowing for repeated treatment. PDT exhibits high therapeutic selectivity towards the lesion, causing little to no damage to healthy tissues, and has only a few toxic side effects. Consequently, PDT is especially suitable for elderly and frail patients who are unable to undergo surgical resection or chemotherapy. In particular, for patients with advanced tumors who have not responded effectively to or are at risk with traditional treatments, PDT is an extremely ideal treatment option.

Different types of molecules can be used as photosensitizers; however, many of them face challenges in clinical application, including limited penetration depth, low solubility, dark toxicity, and a high dependence on oxygen concentration. Therefore, more efficient and safer photosensitizers need to be further studied and developed. Currently, the focus of research and development of novel photosensitizers lies in target modification and smart nanomedicine delivery systems to achieve minimally invasive and specific therapy. An excellent photosensitizer should be capable of achieving precise lesion killing at low doses while having a minimal effect on other parts of the body. In the context of PDT, the application of novel photosensitizers is undoubtedly a key factor in further

improving the therapeutic effect.

Progress The earliest photosensitizers used in PDT were hematoporphyrin derivatives, with the main component being dihematoporphyrin ether (DHE). Sodium porphyrinum, marketed by Canadian company QLT (Quadra Logic Technologies Phototherapeutics Inc.), has received approval for the treatment of bladder, esophageal, and lung cancers. It has become the most frequently used photosensitizer in the PDT of non-cutaneous solid tumors. However, it still has certain disadvantages, such as long-lasting skin photosensitivity and low selectivity for lesion tissues. Subsequently, a wider variety of photosensitizers have been developed for treating various diseases (Table 1). There have been many studies on both traditional and novel photosensitizers.

Porphyrins, chlorins, phthalocyanines, and bacteriochlorin derivatives have been employed as photosensitizers in clinical use (Table 2).
Viscous cycloquinone and metal-ligand anthapurpurin derivatives have entered the clinical research stage as photosensitizers
(Table 3). Meanwhile, research focusing on the development of new photosensitizers is also in full swing. Researchers are developing photosensitizers on the nano platform and achieving better drug delivery effects through surface modifications of the photosensitizer.
They are also aiming to achieve more accurate PDT through the design of activatable and responsive photosensitizers. Furthermore,
they are attempting to overcome the oxygen-depleted microenvironments at tumor sites by developing novel type I photosensitizers and creating photosensitizers more suitable for the treatment of deep solid tumors. Additionally, the combination of PDT with other drugs or therapies, to achieve a better therapeutic effect and reduce drug toxicity and side effects, has also garnered researchers'
interest. Sonodynamic therapy, a derivative of PDT, exhibits higher therapeutic efficiency for deep lesions due to its superior tissue penetration ability. Research on acoustic sensitizer and sonodynamic therapy is also underway.

Conclusions and Prospects PDT is playing an increasingly important role in the treatment of many superficial lesions and cancers. The development of photosensitizers with better treatment effects and fewer toxic side effects has been receiving extensive attention. Researchers have made significant efforts in developing more delicately designed photosensitizers. Many photosensitizers with excellent properties, such as high reactive oxygen quantum yield, high molar extinction coefficient, high maximum absorption wavelength, high targeting ability, low *in vivo* toxicity, and rapid *in vivo* clearance, have been advanced to clinical research.
Simultaneously, more photosensitizers have received marketing approval, benefiting patients. The development of photosensitizers has advanced the diagnosis and precise regulation of diseases, contributing to the development of precision medicine. With the continuous development of novel photosensitizers, PDT will play a greater role in multiple indications and bring benefits to a larger number of patients.

Key words medical optics; photosensitizer; photodynamic therapy; clinical application