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Review

Advances in photosensitizer-related design for photodynamic therapy

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ABSTRACT

Photodynamic therapy (PDT) is highly effective in treating tumors located near body surface, offering strong tumor suppression and low damage to normal tissue nearby. PDT is also effective for treating a number of other conditions. PDT not only provide a precise and selective method for the treatment of various diseases by itself, it can also be used in combination with other traditional therapies. Because PDT uses light as the unique targeting mechanism, it has simpler and more direct targeting capability than traditional therapies. The core material of a PDT system is the photosensitizer which converts light energy to therapeutic factors/substances. Different photosensitizers have their distinct characteristics, leading to different advantages and disadvantages. These could be enhanced or compensated by using proper PDT system. Therefore, the selected type of photosensitizer would heavily influence the overall design of a PDT system. In this article, we evaluated major types of inorganic and organic PDT photosensitizers, and discussed future research directions in the field.

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1. Introduction

Photodynamic therapy (PDT) is a relatively new therapeutic system that, when properly designed and applied, could be highly efficient in treating disease through targeted cell killing and has relatively low adverse effect [1-3]. The cell killing mechanism normally relies on the production of reactive oxygen species (ROS) [4] by PDT agent under the radiation

of light of particular wavelength [5], ROS are a group of strong oxidative reagents capable of seriously affecting the physiological activity of cells and promoting apoptosis [6]. These reactions could be designed to occur only under stimulation of certain wavelengths of light. Hence, even when the PDT agents are absorbed by cells, PDT treatments are generally safe in the absence of light or under weak daylight. In this way, proper PDT therapies are generally regarded to be selective and safe. While most PDT researches focus on

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Table 1 – Examples of application of inorganic photosensitizer-based systems.

Material	Characteristic	Model	Radiation source	Ref.
Bi ₂ S ₃ @Bi Z-scheme	Regulation of electron energy level, and achieved high conversion efficiency	–	808 nm laser irradiation	[20]
Se/N-CDs	Bind RNA selectively, RNA then acted as a carrier to transport photosensitizer to the nucleus of tumor cell	4T1 tumor mice	LED irradiation (550 nm)	[22]
Ru ^{II} -Pt ^{IV} polypyridine Au(I) complexes	Combined with chemotherapy and PTT to improve the effectiveness of cancer treatment	Drug resistant cancers	480 and 595 nm light	[24]
MnFe ₂ O ₄ Cr ₂ Fe ₆ O ₁₂	Metal compounds of Mn and Cr are made to NCs and the release of chemotherapeutic drug was pH-dependent	–	800 nm laser irradiation	[25]
MnFe ₂ O ₄ Cr ₂ Fe ₆ O ₁₂	Metal compounds of Mn and Cr are made to NCs and the release of chemotherapeutic drug was pH-dependent	Michigan cancer foundation-7, breast cancer cells	UV light	[27]
g-C ₃ N ₄ & PEG	This nanoplatform could produce oxygen via water splitting, and turn oxygen into ROS under light. It also improved biocompatibility due to the PEG modification	A-431 tumors	blue light	[29]
CuS	Does not produce ROS, but can be used as an excellent carrier of photosensitizer to achieve the combination of PTT and PDT	L929 normal fibroblast cells and HeLa cells	808 nm laser irradiation	[30]
Iridium (III) complex	Self-assembled by electrostatic force with HA to form a spherical nanostructure called Irpy-HA, which is highly stable (keep its nanostructure at least 30 d).	4T1.2 cells	532 nm light	[31]
BPNS-GNBP	Act as carriers in PDT, and combined with PTT in the treatment of deep-seated tumor	HeLa cells	808 nm laser irradiation	[34]

cancer treatment [7], PDT systems also have other clinical applications such as disinfection and skin disease treatment [8]. In general, PDTs are versatile and effective when used properly. Because it is relatively new in clinical application, there are still plenty of potential for further developments [Table 1, 2 and 3].

In PDT research, photosensitizers development is a major theme because of its importance. Photosensitizer is the substance that produces active intermediates when exposed to light [9,10], with some being able to show photo rejuvenation *in vitro* and *in vivo* [11]. Hence, the light-conversion efficiency of the photosensitizer largely determines the overall light-conversion efficiency of the whole PDT system [12]. The light-induced products generated by the photosensitizer also provide the starting point for the PDT to exhibit therapeutic effects. Therefore, photosensitizers are the core of a PDT system [13], and the choice of photosensitizer is highly-dependent on the purpose of the specific PDT. Apart from a well-selected photosensitizer, the other main factors affecting PDT efficiency are oxygen content (especially in tumors microenvironment [14]) and photosensitizer accumulation at target sites [15]. In most cancer PDT, ultimate photodynamic efficacy is supported by these 3 main factors. Hence, photosensitizers that are easily applicable to different delivery platforms are more favorable [16].

Although various types of photosensitizers are available, studies have shown that two major types of photosensitizers generally display excellent curative effects in PDT. These are: (1) inorganic nanoplatform, (2) porphyrin and porphyrin derivatives (including porphyrin precursors). These photosensitizers all have their unique characteristics, advantages and disadvantages. Delivery systems are often used to enhance their effect and improve their unfavored properties, which could result in decisive changes. Hence, it

is important to design the photosensitizer, delivery system, and other related factors such as methods of administration, as integrated therapeutic strategy. In the following text, we will present more detailed descriptions of and discussions about some of the recent advances of PDT systems using these types of photosensitizers.

2. General properties of photosensitizers and correspondent PDT systems

Photosensitizer converts light into other forms of energy [17], such as heat energy and chemical energy [18]. During this process, other substances may be produced due to the interaction between substances in the environment and activated photosensitizer itself or released energy. The released energy and/or produced substance (normally ROS) thus could exhibit therapeutic effects. In this way, in areas where both light and photosensitizer could reach, certain medical purposes are achieved.

Based on this mechanism, some essential demands must be carefully counted in order to design clinically applicable PDT agents. First, because the PDT agent needs to locate to target tissue in order to be activated *in situ*, it is important for them to be biocompatible, and be able to be removed from the body or degraded later on. This is normally less a concern for porphyrin-based photosensitizers, but could be a problem for inorganic photosensitizers. Second, the agent should have adequate light conversion efficiency (and/or release more medically effective substances), otherwise impractical strength of light radiation will be required to exert demanded medical effects; in addition, the ability of photosensitizer to be active by specific wavelength of light is sometimes important as light with certain wavelengths could penetrate deeper into tissues. Here, inorganic photosensitizers often possess some

Table 2 – Photosensitizer system of Porphyrin and porphyrin derivatives (including porphyrin precursors).

Photosensitizer system	Treatment effect	Combo	Radiation source	Ref.
CuS@ICG	This system aims to both kill tumor cells and disrupt the tumor microenvironment for enhanced tumor suppression	PDT and PTT	808 nm laser	[30]
Ppa	Ppa is a derivative of chlorophyll, which are the most abundant natural photosynthetic pigments	–	660 nm-light irradiation	[41]
	Responsive NPs including Ppa was designed, It could intelligently release ROS	–		[42]
	The photosensitizer Ppa was functionalized with a ¹ O ₂ -responsive vinylthioether	–		[43]
Chlorin I & II	The structures of those two compounds are also stable under photo-bleaching test, and <i>in vivo</i> assessments displayed that they both have high tumor selectivity	–	Absorption peak around 650 nm	[44]
NP-sfb/ce6	This system is a combination of immunotherapy and PDT, and it appears that the synergistic treatment of tumor is more effective than single cancer treatment	PDT and immunotherapy	660 nm-light irradiation	[46]
5-ALA	5-ALA, a precursor of porphyrin, is reported to delay glioma progression and is expected to have great potential in PDT.	–	410, 510, 545, 580 and 630 nm under	[49]
	A nano delivery system where 5-ALA is loaded on PMO with PB coating (PB@PMO-5-ALA), It increased PpIX level in glioma cells by 75% comparing with unprotected 5-ALA in mice.	–	405 nm + 505 nm light source, 5-ALA as photodynamic drug produced the most ROS	[52]
PMO-PpIX	5-ALA may also be used in the treatment of certain skin tumors such as SCCs	Activate immune response	Illuminated with green laser light (532 nm)	[53]
	The PMO load PpIX by amide bond, and this structure showed better tumor inhibition <i>in vitro</i> than free PpIX	–		[55]
PA-Apt-CHO-PEG	PA was first linked to aptamer, and the PA-aptamer molecules were then combined with PEG to form circular PA-aptamer-PEG. The nanostructure is stable in normal physiological environment and bonds breaking in the acidic tumor microenvironment.	pH-dependent	670 nm light	[57]
COF-366	This NPs provide the combined therapy of PTT and PDT under a single wavelength light illumination with the monitoring of photoacoustic imaging, and makes the operation simpler and more convenient	PDT, PTT and photoacoustic imaging-guided	635 nm laser	[60]
Ag-MOFs@ TCP	This structure was constructed by decorating AgNPs onto the porphyrinic PCN and further camouflaging with the NM with inflammatory targeting ability (PAM)	PDT, PTT and metal ion therapy	660 nm light irradiation	[64]
TAT+AzoNPs@(Ce6+TPZ)	This system include TAT (targeting peptide), Ce6 (photosensitizer), TPZ (hypoxia activatable prodrug) and PEG-Azo-PLGA (amphiphilic polymers linked by azobenzene), which could induce hypoxia in tumor tissue under light stimulation by the releasing of TPZ.	PDT, chemotherapy and controlled drug delivery system	660 nm light irradiation	[65]

advantages as they usually convert energy more efficiently. Third, for further improvement of overall therapeutic effect, sometimes it is important to modify the pharmacodynamics of the photosensitizers, increasing their concentration at target sites; and/or use PDT in combination with other drugs/therapies. For this purpose, various multifunctional PDT systems are often fabricated.

In summary, designing a proper PDT agent requires careful evaluation of a number of factors, and focusing on the clinical purpose of the PDT therapy. It is important to choose/generate the optimal photosensitizer and applying supportive

strategies to compensate its disadvantages and exploit its advantages. In the next sections, some recent interesting PDT systems using different types of photosensitizers will be reviewed, demonstrating our advances in this field.

3. Inorganic photosensitizer-based systems

As introduced, inorganic photosensitizers often have high light conversion efficiency but suffers from poorer biocompatibility [19]. Here, the studies presented below

Table 3 – Examples of PDT for non-cancer diseases and conditions.

Medicine	Research	Therapeutic purposes	Radiation source	Ref.
Tribenzoporphyrazines	This photosensitizer displayed high killing efficiency against <i>S. aureus</i> (and potentially other Gram-positive bacteria), and it showed improved bacteria cell wall permeability	Diseases caused by drug-resistant bacteria such as <i>S. aureus</i>	660 nm light irradiation	[67]
TiO ₂ /Zn-HY	Inorganic photosensitizer complex which uses TiO ₂ NPs doped with Zn and hypericin.	Cutaneous <i>Leishmaniasis</i> caused by parasite <i>L. amazonensis</i>	Visible light	[68]
NE-CUR	A NE-CUR has devised which enhances performance of curcumin in PDT against vulvar intraepithelial neoplasia induced by HPV.	Intraepithelial neoplasia of vulva caused by HPV infection	Operating at 447±10 nm	[69,70]
5-ALA	An effective 5-ALA based PDT system to treat MRSA infected wounds of diabetic mice, PDT kills bacteria with a mechanism that is different from antibiotics	Infection caused by drug-resistant bacteria such as MRSA-infected diabetic wounds	635 nm irradiation	[71]
Methylene blue	A clinical report describes a case of palatal ulcer that is not sensitive to antibiotics but responds well to PDT and PBMT	Palatal ulcer	660 nm-light irradiation	[72]
5-ALA with MN	A clinical trial involving 41 AA patients, most of the patients treated with this PDT approach showed reduced severity of their symptoms	Immune-mediated disorder such as AA	630 nm irradiation	[73]

employed various strategies (some of which are fairly interesting) to maintain the high efficiency and/or solve the biocompatibility problem of inorganic photosensitizers with some success.

3.1. Novel inorganic photosensitizers

During light activation, the conversion of energy is accompanied by the transition of electron bands. Exploiting this transition, Zhang et al. reported novel Bi₂S₃@Bi Z-scheme heterostructured nanorods. Their work simultaneously implemented spatiotemporally synchronous O₂ self-supply and production of ROS for hypoxic tumor therapy. The hole of the Bi₂S₃ valence band can react with water to supply O₂ for the electron on the conduction band of Bi to produce ROS (Fig. 1A and 1B) [20]. The regulation of electron energy level makes it easier for electrons to be excited and then produce ROS [21]. By using this design of Bi₂S₃@Bi Z-scheme, they achieved high conversion efficiency, the production of oxygen and ROS was about twice than that of Bi₂S₃ (Fig. 1C-1E).

Du et al. have produced Se/N-doped carbon dots, which inhibit tumor growth by destroying DNA of tumor cell. Here, the photosensitizer Se/N-doped carbon dots were shown to bind RNA selectively. RNA then acted as a carrier to transport photosensitizer to the nucleus of tumor cell, and released ROS under light irradiation. Se/N-CDs near the nuclear membrane produced ROS that damaged the membrane under light irradiation, permitting the entry of more Se/N-CDs and thereby improving the conversion efficiency of photosensitization (Fig. 2) [22]. The system exhibited tumor inhibition effect with low organ damage with in model animals. Although the ¹O₂-generating efficiency of Se/N-doped carbon dots (10.6%) is lower than commercial photosensitizer, the nucleus-targeting mechanism is novel and sheds new lights on cancer treatment strategy.

Another class of inorganic photosensitizers is the inorganic coordination compounds. Theoretical studies have shown that inorganic coordination compounds have certain phototransmissibility. For example, a study by Rende et al. have determined the main photophysical properties of some unsubstituted and iodine substituted phosphorus corrole complexes (Fig. 3), and the results showed that these compounds can indeed be employed as photosensitizers in PDT [23]. Here, density functional theory and its time-dependent formulation was applied to compute the photophysical properties (including photodynamic) of a series of unsubstituted and iodine substituted phosphorus corrole complexes. This study showed the benefit of using theoretical calculation as a guide to reduce screening experiments in the development of PDT drugs.

Some metal ions complexes are widely used in chemotherapy for cancer treatment. Among them, polypyridine complexes have also gained much attention as photosensitizers for use in PDT. Hence, chemotherapy using metal ions could be combined with PDT to improve the effectiveness of cancer treatment. Gasser group have reported one such system using a Ru^{II}-Pt^{IV} polypyridine complex conjugate to treat drug resistant cancers. Because each component in this system has its individual targets, this system is multi-targeting and multi-action. It successfully produced strong cytotoxicity in drug resistant tumor cell upon 595 nm light irradiation [24].

Au, another metal antitumor reagent, could also be combined with PDT to expand the therapeutic potential of photosensitizers to dual potency cytotoxic agents. Elena et al. have introduced a photosensitizers system which was derivatives of bacteriopurpurin with thiolated Au(I) complexes, to realize a deep-seated tumor therapy program that can be activated by light (Fig. 4) [25]. Photosensitive systems that introduce metal ions can also be combined with

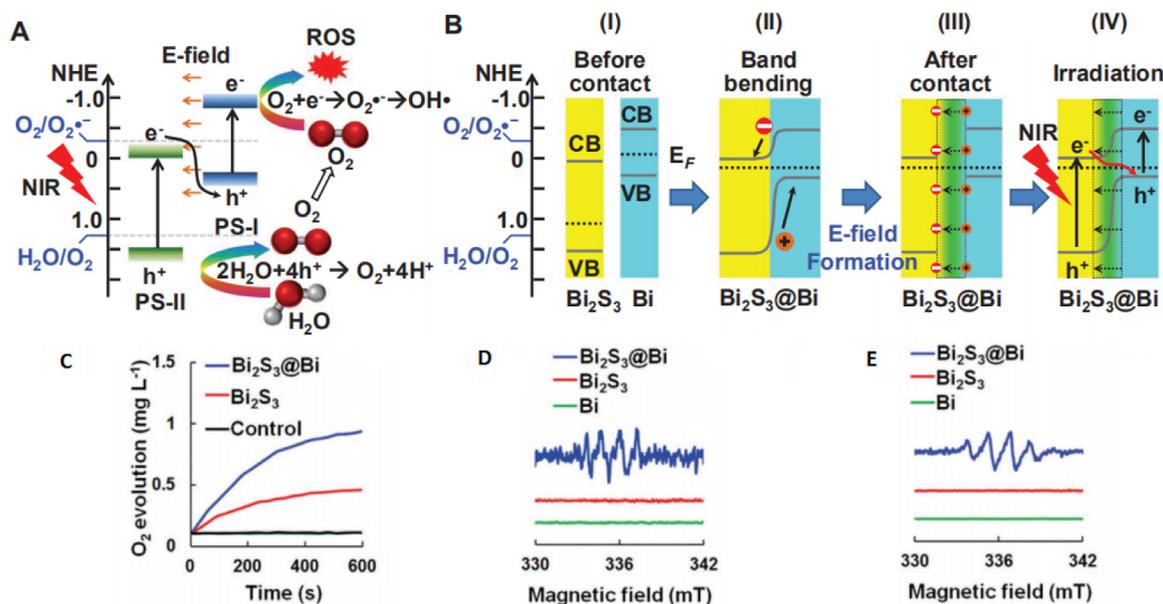


Fig. 1. – (A, B) Diagram of electron energy level change under NIR radiation. (C) O₂ generation curve, (D) ESR spectra O₂⁻(DMSO), (E) OH⁻(water). Reproduced with permission from [20]. Copyrights 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

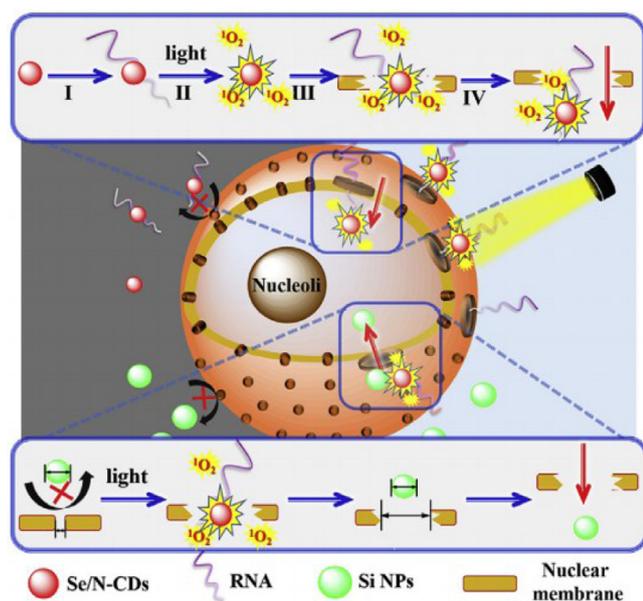


Fig. 2. – Schematic diagram of light induced nanoparticles larger than nuclear pore into nucleus. Reproduced with permission from [22]. Copyrights 2019 Elsevier Ltd.

chemotherapy and photothermal therapy (PTT) to enhance therapy [26].

Some other studies directly used metal compounds as photosensitizers for PDT. MnFe₂O₄ and Cr₂Fe₆O₁₂ nanocarriers (NCs) has been used as a photosensitizer in some reports to deliver chemotherapeutic drug such as curcumin and provide a new structure for PDT by Hossein et al. [27]. In this study, the metal compounds of Mn and Cr are made to NCs and the release of chemotherapeutic drug

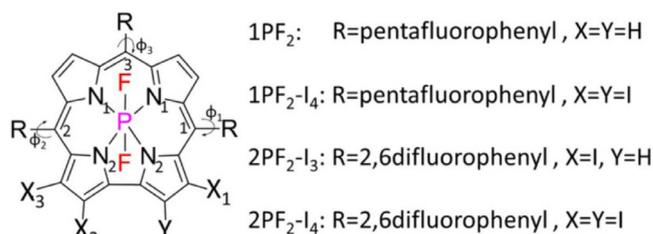


Fig. 3. – The main geometric parameters and chemical composition of the system studied. Reproduced with permission from [23]. Copyrights 2020 Wiley Periodicals, Inc.

from NCs was pH-dependent (Fig. 5). According to the author, chemotherapeutic drug release from Mn compound can reach to over 90% at acidic media instead of 41% at neutral media. Therefore, the MnFe₂O₄ NC is proposed to be used as a pH-responsive carrier to deliver chemotherapy drugs in acidic tumor microenvironment, as well as a photosensitizer for PDT. This study provides new ideas for further research on multifunctional photosensitizer in PDT.

3.2. Modifications of inorganic photosensitizers and photosensitizer delivery options

Moreover, inorganic nanomaterials generally have poor biocompatibility [28], so it generally requires certain modification such as the addition of the widely used poly ethylene glycol (PEG) chain. Cai et al. developed a photosensitizer called graphite phase carbon nitride (g-C₃N₄) and modified it with four-arm-PEG [29]. This nanoplatform was named AGCN-PEG (Fig. 6), which could produce oxygen via water splitting, and turn oxygen into ROS under light. It also improved biocompatibility due to the PEG modification.

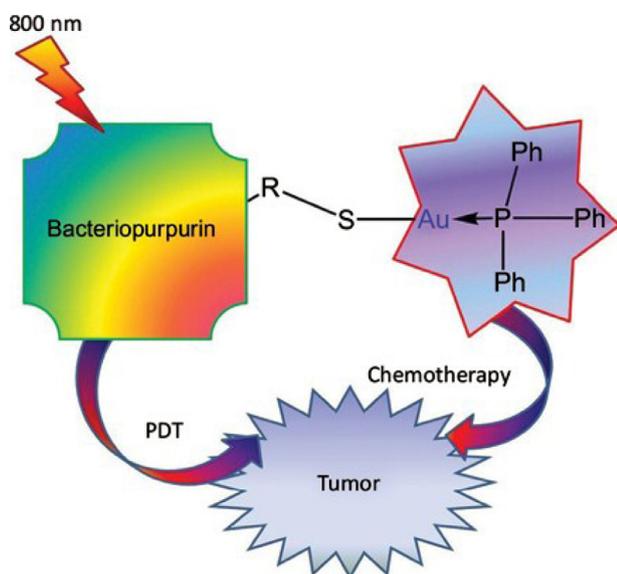


Fig. 4. – Schematic diagram of PDT combined with chemotherapy with photoactivation. Reproduced with permission from [25]. Copyrights 2021 Bentham Science Publishers.

The researchers have compared the AGCN-PEG with PMPyP4, and while almost no ROS was produced in TMPyP4 group under hypoxic conditions, AGCN-PEG displayed a strong ability to produce ROS under the same conditions.

Beyond that, hyaluronic acid (HA) is an alternative modification choice. Gai et al. developed a nano platform called honeycomb MnO_2 , and used it to load the photosensitizer such as CuS nanoparticles (NPs) and indocyanine green (ICG). The particles were then wrapped in HA to grant the nano platform the capability to specifically bind CD44 on tumor cells [30]. In this experiment, the honeycomb MnO_2 is not only the carrier of photosensitizer, but also the oxygen provider for PDT and heat generator of

PTT. This system aims to both kill tumor cells and disrupt the tumor microenvironment for enhanced tumor suppression (Fig. 7). The highlight of this article is the high drug load rate, of which CuS NPs showed nearly 66.8% and ICG molecules showed up to 80.22% load rates. This system also showed good tumor inhibition in Kunming mice and no obvious damage was found in viscera.

In another study by Li et al., an iridium (III) complex (Irp) self-assembled by electrostatic force with HA to form a spherical nanostructure called Irpy-HA, which displayed excellent ability of singlet oxygen ($^1\text{O}_2$) generation [31]. Similarly, the HA target to the CD44 receptor in tumor cell membrane to enhance internalization and selective disassemble. After which, the iridium (III) gathered in mitochondria and produced the singlet oxygen under the green light irradiation (Fig. 8). The nanosphere of Irpy-HA is highly stable under condition, which can keep its nanostructure at least 30 d *In vitro* tumor cell experiment, over 90% tumor cells exhibited apoptosis and necrosis after PDT using Irpy-HA.

The limitation for medical application of many inorganic nanomaterial is their poor water solubility [32]. This could also be improved by proper modification. Cai et al. have reported a photosensitizer system of PDT that uses tunable water-soluble carbon nitride with alkali-metal cations modification. In this construct, $\text{g-C}_3\text{N}_4$ is only about atomic-thickness so that it can dissolve easily in water with alkali Zn^{2+} and K^+ modification (Fig. 9). Then water-soluble $\text{g-C}_3\text{N}_4$ can tune the absorption edge from 460 nm to the entire visible-light region (663 nm), and reduce the band gap to 1.94 eV. It is worth mentioning that the synergistic effect of $\text{g-C}_3\text{N}_4$ and alkali metal ion have improved the production efficiency of ROS (45.16% vs $\sim 7.95\%$ of pristine $\text{g-C}_3\text{N}_4$) [33]. This study accomplishes a considerable inactivation efficiency of virulent melanoma A375 by inhibiting the over expression of glutathione (GSH), and the authors claimed that they have overcome the limitation of $\text{g-C}_3\text{N}_4$ as a photosensitizer of PDT and revealed its multifunctional promise to cancer therapy.

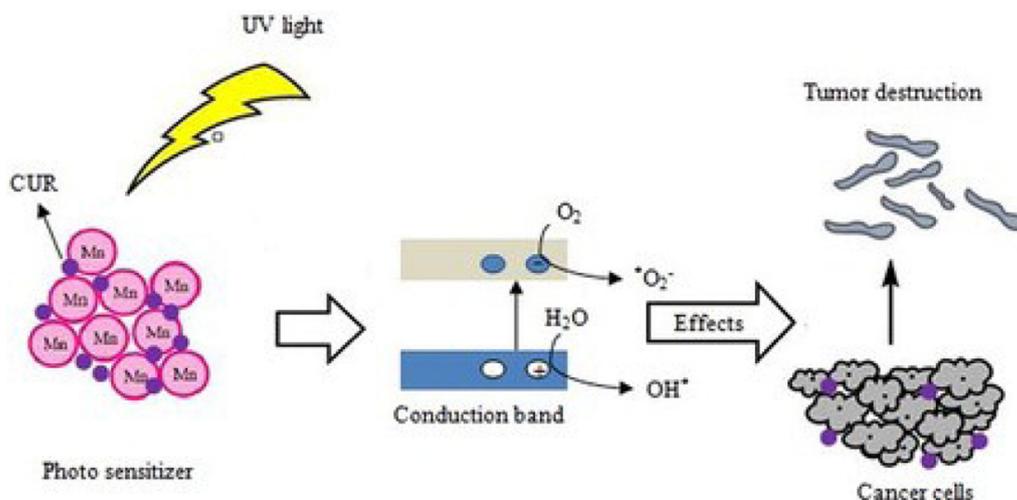


Fig. 5. – Schematic diagram of PDT photosensitizer system of Mn compound with photodynamic agent and pH response. Reproduced with permission from [27]. Copyrights 2021 Informa UK Limited.

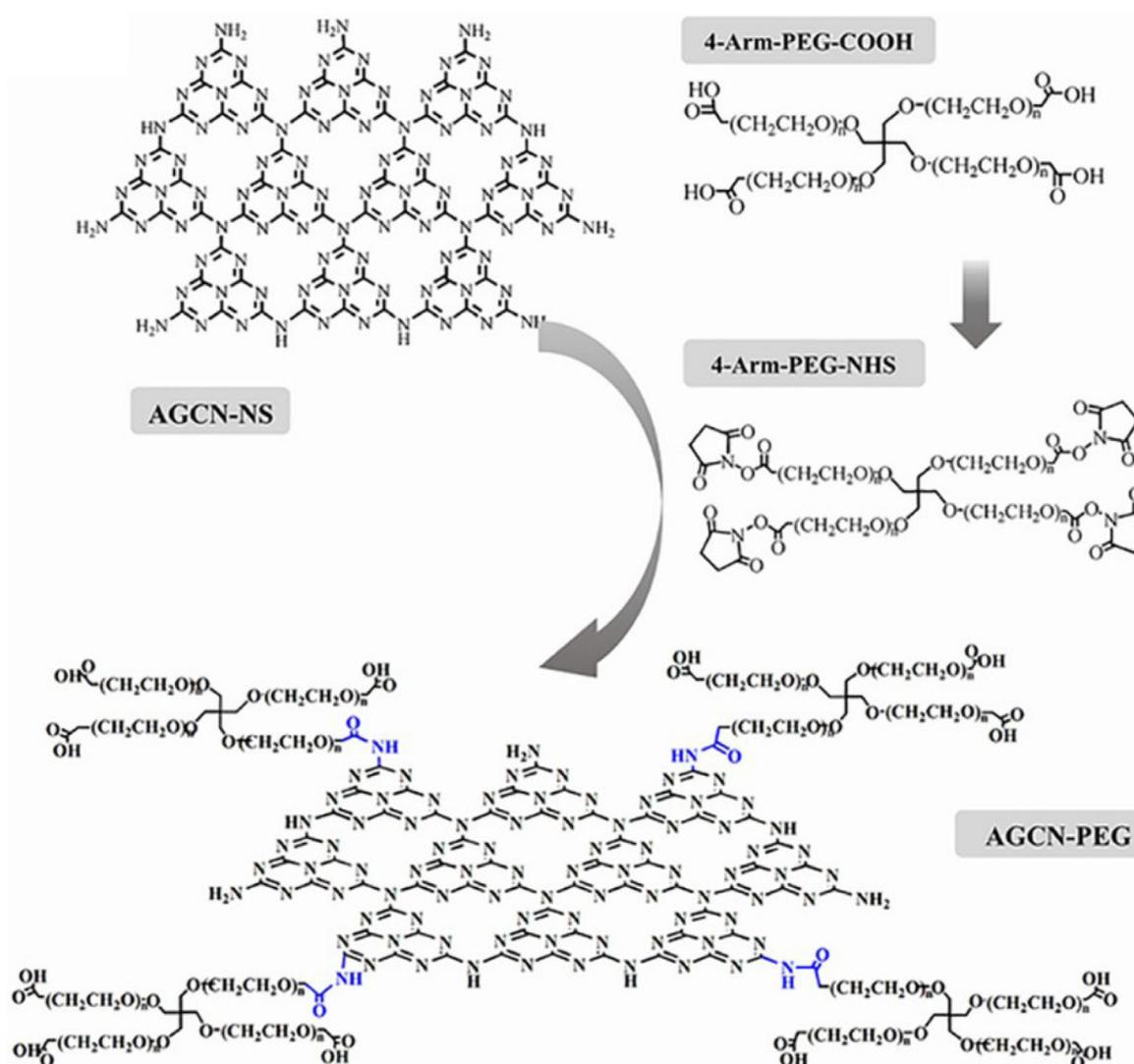


Fig. 6. – Characterization and preparation of four arm PEG-COOH. The structure diagram and principle of AGCN-NS modified by four arm PEG-COOH. AGCN-NS covalently binds to PEG via amide bond (blue). Reproduced with permission from [29]. Copyrights 2020 Elsevier Inc.

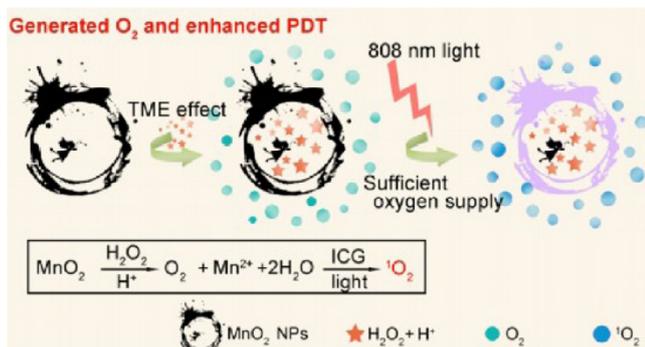


Fig. 7. – Schematic diagram of the formation of O_2 and further formation of 1O_2 catalyzed by MnO_2 in HA/ICG-CuS@hMnO₂ under near-infrared light of 808 nm. Reproduced with permission from [30]. Copyrights 2020 Elsevier B.V.

Except for being used as photosensitizers, some inorganic nanomaterials can also act as carriers in PDT. Lu team used black phosphorus nanosheets (BPNSs) to load gold nanobipyramid (GNBPs) and enhanced the curative effect of deep-seated orthotopic lung tumors [34]. The BPNS-GNBP system could simultaneously enhance 1O_2 generation and hyperthermia by localized surface plasmon resonance (LSPR) in cancer therapy to overcome the problem of low 1O_2 level at deep tumor tissue (Fig. 10). Results showed that BPNS-GNBP exhibited a higher photothermal conversion efficiency than only BPNS or GNBP, and the combined effect of PTT and PDT by this system also improved the overall tumor inhibition effect.

3.3. Summary

It is clear from above studies that there are still numerous possibilities and huge potential for inorganic photosensitizer

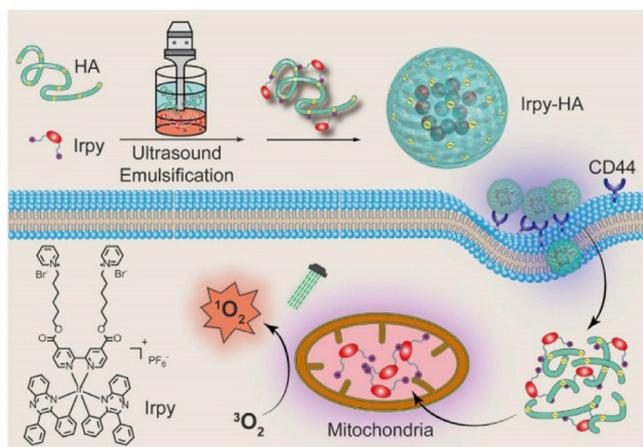


Fig. 8. – Schematic of Irpy-HA for PDT in this study. Reproduced with permission from [31]. Copyrights 2019 Elsevier Ltd.

development. The strategies that could combine light-conversion, tissue targeting, and/or drug delivery probably will become more attractive in future research, especially for tumor treatment. However, simpler designs with high efficiency will also have their clinical application scenarios (e.g. surface disinfection) as they could be more cost-effective and easier to use.

4. Porphyrin and porphyrin derivatives

Porphyrin is a family of light-absorption molecules with very ancient origin [35]. It is believed to be one of the first batch of biological molecules utilized by life on earth, and played vital part in the evolution history [36]. Chemically, porphyrins are organic molecules made up of 4 nitrogen-containing rings [37], which can form complexes with metal ions [38]. Because of its unique light-absorption capability, it forms essential component of omnipresent biomolecules like chlorophyll and heme, which are categorized as porphyrin derivatives.

Thus, porphyrins are generally safe, though extremely high level of porphyrin inside of body could lead to porphyria. In fact, almost all organic photosensitizers are either porphyrin derivatives or molecules share very similar structures and mechanisms with porphyrins. However, porphyrins in their original forms generally have poor photodynamic activity, hence PDT systems mostly uses porphyrin derivatives, which could have higher efficiency, as the photosensitizer [39]. For example, chlorophyll and heme are widely used in PDT, since both are endogenous products of natural organisms with superior biocompatibility and high efficiency [40]. Below, we will review various strategies to further improve clinical performance of porphyrin-based PDTs such as using modified porphyrin derivatives or porphyrin precursors, designing specific delivery vehicle, and applying combined therapies.

4.1. Novel porphyrin derivatives and porphyrin precursors

Zhang et al. have reported a photosensitizer that combines the block copolymer with pyro pheophorbide a (Ppa). Ppa is a derivative of chlorophyll, which are the most abundant natural photosynthetic pigments [41]. This photosensitizer is named POEGMA-b-P (MAA-co-VSPpaMA), which could intelligently release ROS when the host NPs accumulate in tumor tissue and is dissolved by cancer cells [42]. The photosensitizer Ppa was functionalized with a $^1\text{O}_2$ -responsive vinyl dithioether [43] (Fig. 11). Besides, the linker of the Ppa and block copolymer is sensitive to ROS which would accelerate the break down process when ROS is generated. Therefore, they claimed their system as a self-amplified PDT.

Chen et al. have developed a few photosensitizers of another type of porphyrin derivatives called chlorin (i.e. 5,10,15,20-tetraphenylporphyrin and its substitution products). In their work, they generated novel photosensitizers such as 5,10,15,20-tetraphenyl-[2:3]-[(methoxycarbonyl,carboxy) methano] (named chlorin I) and 5,10,15,20-tetraphenyl-[2:3]-[(methoxycarbonyl, (2-hydroxyethyl) amide] methano] (named chlorin II) (Fig. 12). They characterized the structure of chlorin I & II with UV-vis, HNMR, CNMR and HRMS spectroscopies. The structures of



Fig. 9. – Schematic of the preparation for $\text{Zn}^{2+}, \text{K}^+ - \text{C}_3\text{N}_4$ nanosheets. Reproduced with permission from [33]. Copyrights 2020 Elsevier B.V.

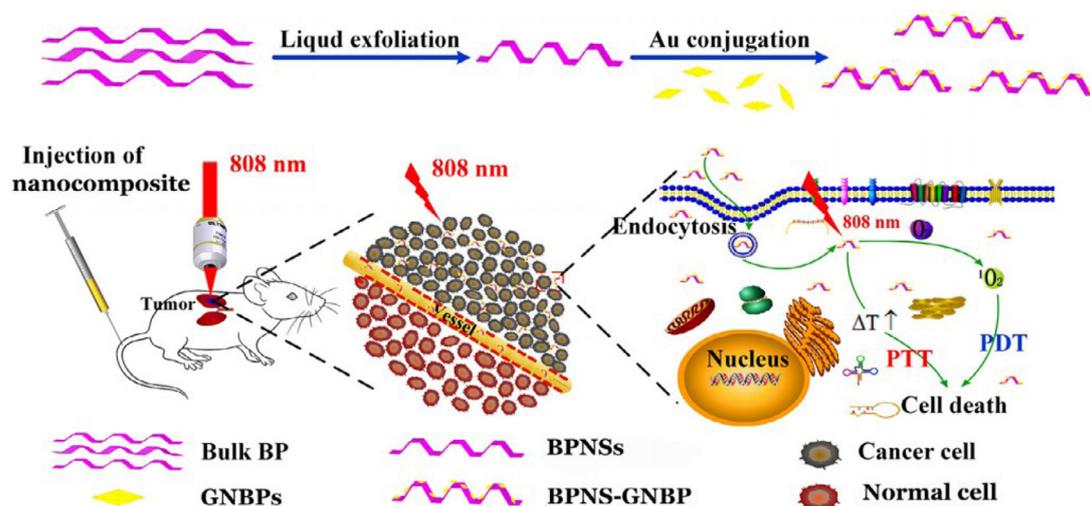


Fig. 10. – Preparation and application of LSPR and GNBP-BPNS nanocomposites reinforced PTT-PDT. Reproduced with permission from [34]. Copyrights 2020 Acta Materialia Inc, Published by Elsevier Ltd.

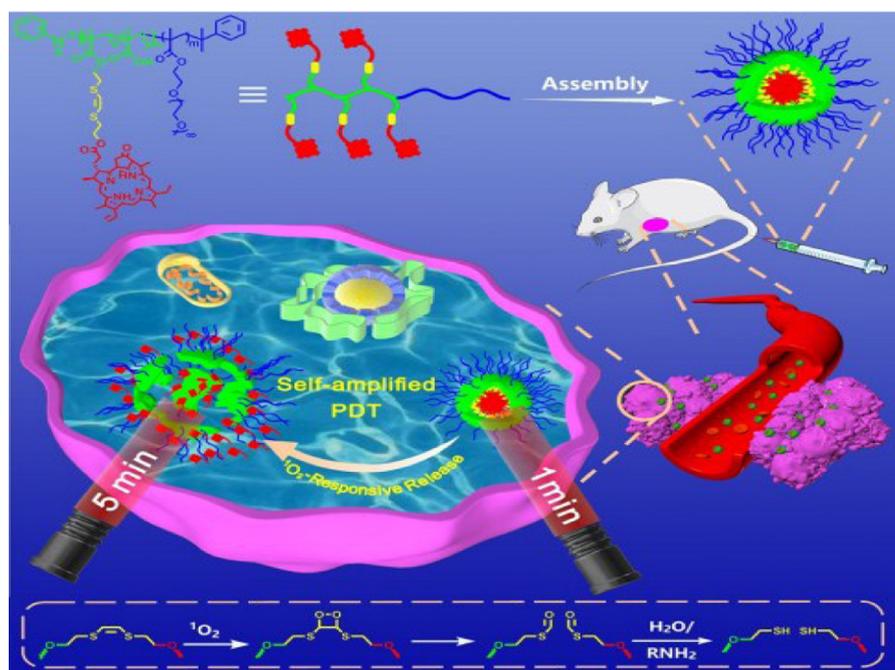


Fig. 11. – Schematic of autoamplification PDT in NIR and mechanism of $^1\text{O}_2$ stimulation of cleavage. Reproduced with permission from [43]. Copyrights 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

those two compounds are also stable under photo-bleaching test [44]. Spectrometry analysis results showed that chlorin I and II both have an absorption peak around 650 nm. *In vivo* assessments displayed that both chlorin I and II have high tumor selectivity, and could induce tumor cell apoptosis under 650 nm laser irradiation. Both compounds displayed low tissue damage in histological examination, which was possibly benefited from their tumor selectivity. After comparing these two chlorin derivatives, the authors concluded that chlorin I suppresses tumor more effectively making it more appropriate to be developed as a potential anticancer photosensitizer agent.

The chlorins can not only be used directly as a photosensitizer, but also as a carrier of other drugs [45]. Under such circumstances, the chlorin carrier system can play double roles in tumor therapy of PDT. Sun group have reported such a PDT system where sorafenib (Sfb) and chlorin e6 (ce6) were co-loaded in a NP which is responsive to ROS (NP-sfb/ce6) [46]. Sfb is an effective tumor suppressor, which could induce T cell-dependent local and systemic antitumor immune responses in organisms where CD8^+ T cells quickly proliferate to kill the tumor cells. In this system, ROS produced by ce6 under 660-nm laser irradiation could destruct the NPs and release Sfb while the generated ROS

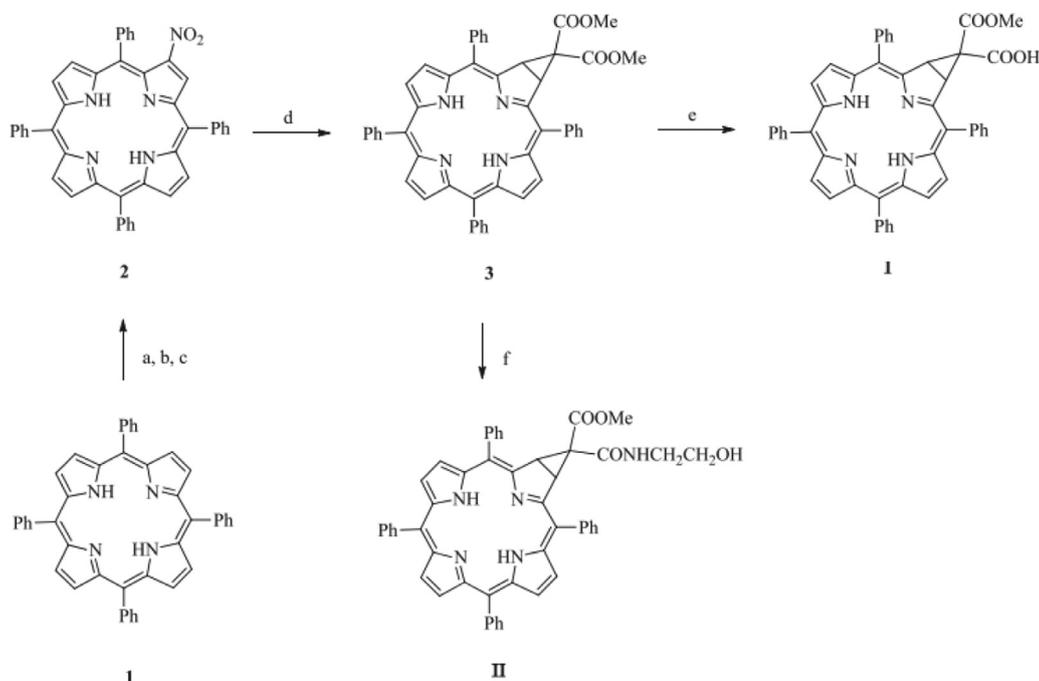


Fig. 12. – The flowchart of synthetic of chlorin I and chlorinII, a, b, c, d, e, f are available in references. Reproduced with permission from [44]. Copyrights 2020 Elsevier Masson SAS.

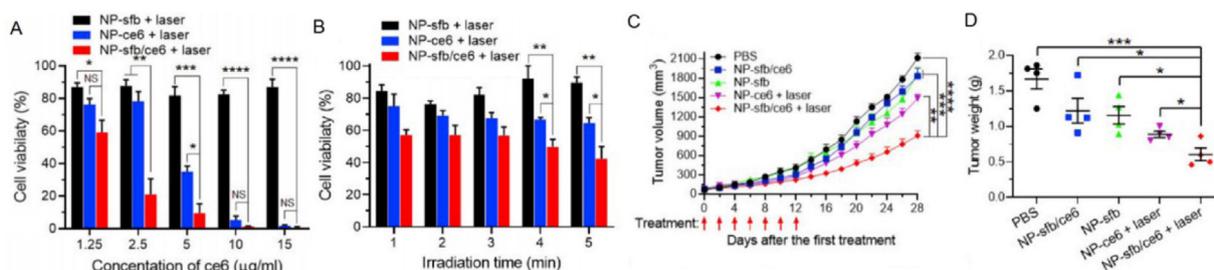


Fig. 13. – (A, B) Evaluation of *in vitro* effects for NP-sfb/ce6 in PDT. (C) K1-Tumor growth curve after the first treatment. (D) The weights of K1-tumors after the treatment. Reproduced with permission from [46]. Copyrights 2020 Elsevier Ltd.

can kill tumor cells at the same time. Therefore, this NP-sfb/ce6 system is a combination of immunotherapy and PDT and it appears that the synergistic treatment of tumor is more effective than single cancer treatment (Fig. 13). Hence, this combination strategy for tumor treatment shows good potential for improving antitumor effects of PDT.

Glioma is a malignant brain tumor with extremely low 5-year survival rate and high recurrence [47]. Due to its sensitive location, glioma is often very difficult to treat [48]. Recently, 5-aminolevulinic acid (5-ALA), a precursor of porphyrin, is reported to delay glioma progression and is expected to have great potential in PDT [49]. It is shown that 5-ALA can be transformed into protoporphyrin IX (PpIX) *in vivo*, which is a highly effective photosensitizer like the heme and can produce free radicals and ROS with 635 nm laser light excitation. One problem of 5-ALA is that untransformed 5-ALA could induce edema in the tissue, especially under high doses of light about 635 nm (Fig. 14A). Because PpIX has 5 absorption wavelength peaks (410, 510, 545, 580 and 630 nm), hence using weaker multiple wavelength lights can

improve the efficiency of 5-ALA based PDT and reduce toxicity. Based on this principle, Morita group developed a flexible light-emitting diode unit to improve 5-ALA PDT effects by emits light of multiple wavelengths. In this article, under 405 nm + 505 nm light source, 5-ALA as photodynamic drug produced the most ROS (Fig. 14B). The results showed that more ROS were produced at dual wavelengths so that the effect of PDT is better under the synergistic action [50].

Tough 5-ALA has emerged as a promising modality for localized glioma ablation with limited damage to healthy brain tissues in experimental models, its inability to penetrate blood brain barrier (BBB) to reach glioma sites and hypoxic tumor microenvironment in glioma (low oxygen content in tumor site is an important factor restricting PDT [51]) hamper practical applications of 5-ALA based PDT. To solve these problems, Lu team designed a nano delivery system where 5-ALA is loaded on periodic mesoporous organosilica (PMO) with Prussian blue (PB) coating (PB@PMO-5-ALA) [52]. These NPs are ~81 nm in diameter and displayed good biocompatibility. It increased PpIX level in glioma cells by 75% comparing

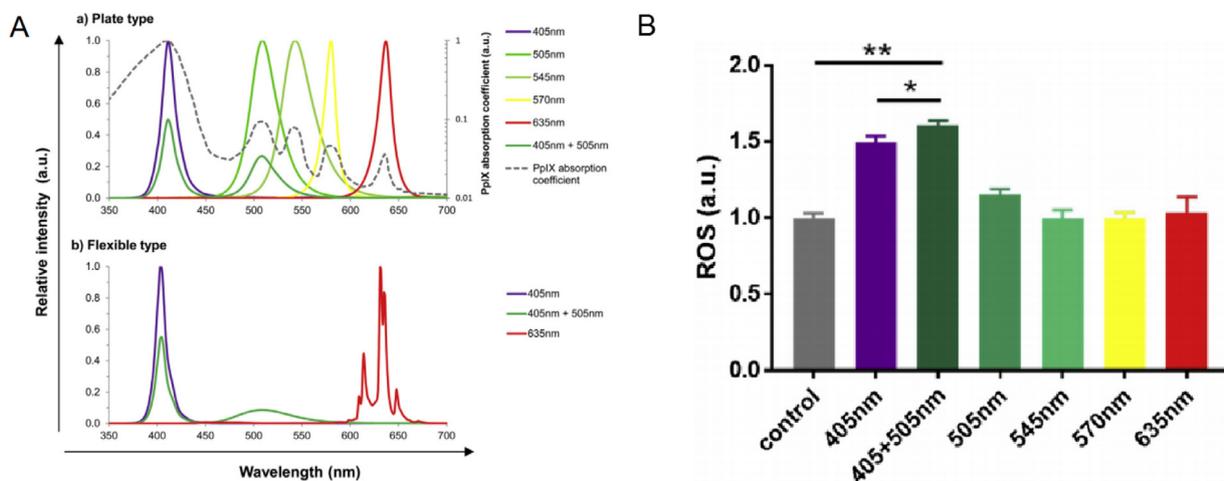


Fig. 14. – (A) Relative spectral distribution of the plate-type LEDs (a) and flexible-type LEDs (b). (B) ROS produce by PpIX under different light sources. Reproduced with permission from [50]. Copyrights 2019 Japanese Society for Investigative Dermatology, Published by Elsevier B.V.

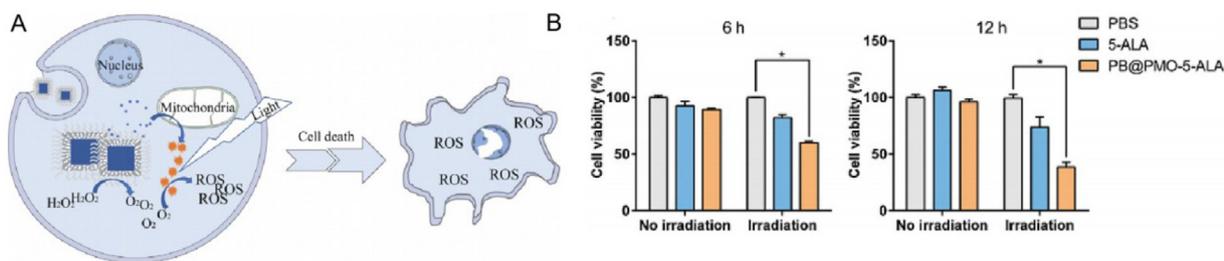


Fig. 15. – (A) Decompose H₂O₂ to O₂ in a temperature responsive manner, and increase the O₂ in tumor site, then the tumors were killed by PDT. (B) Evaluation of *in vitro* effects for PB@PMO-5-ALA in PDT. Reproduced with permission from [52]. Copyrights 2020 Elsevier Inc.

with unprotected 5-ALA in mice, and effectively decompose hydrogen peroxide to oxygen in a temperature responsive manner (Fig. 15). The results from this study encourages further investigation of 5-ALA based glioma therapies.

5-ALA may also be used in the treatment of certain skin tumors. Squamous cell carcinoma (SCCs) is a type of skin tumor with high incidence and a study from Wang group reported a PDT system using 5-ALA could inhibit this type of tumor efficiently. In this work, exosomes derived from ALA-PDT-treated SCCs were incubated with SCCs, fibroblasts and immature dendritic cells (DCs), separately discovered that exosomes derived from PDT-treated SCCs have ability to induce DCs maturation and IL-12 secretion, and promote the secretion of TGF- β 1 from fibroblast, which improve anti-tumor immunity of the model animals (Fig. 16) [53]. This study revealed a novel PDT-enhanced immune reaction against cancer cells, and provides a promising PDT strategy for treating SCC.

4.1. Delivery systems for porphyrin-based PDT

However, there is a practical problem for many porphyrin derivatives, as they generally have high protein affinity. Together with their high biocompatibility (due to their

biological origin), they could spread in the whole body and sometimes stay in the body for too long by attaching to albumin and simultaneously avoiding macrophages clearance. This is an undesirable situation because the long-term accumulation of porphyrin derivatives in non-tumor tissues could lead to allergic symptoms under natural light. Therefore, drug delivery systems that could improve the biodistribution of porphyrin photosensitizers and increase their accumulation at tumor sites are important for clinical application.

One way to generate such delivery system is developing highly functional materials. Lee group successfully developed an innovative PMO structure to encapsulate the PpIX for this purpose (Fig. 17A). PMO is a class of materials based on organic as well as inorganic hybrid nanocomposites, which has a considerable number of mesoporous and good biocompatibility. This structure was organo-bridged silsesquioxane ((R'O)₃Si-R-Si(R'O)₃)-integrated mesoporous silica frameworks, which have the provision of active sites for subsequent surface functionalizations [54]. In addition, PMO materials often have various available reactive groups that can be modified with other functional molecules to further improve their performance such as drug loading capacity and biocompatibility (like PMO-OH(II)-NH₂ [55]). In this study, the

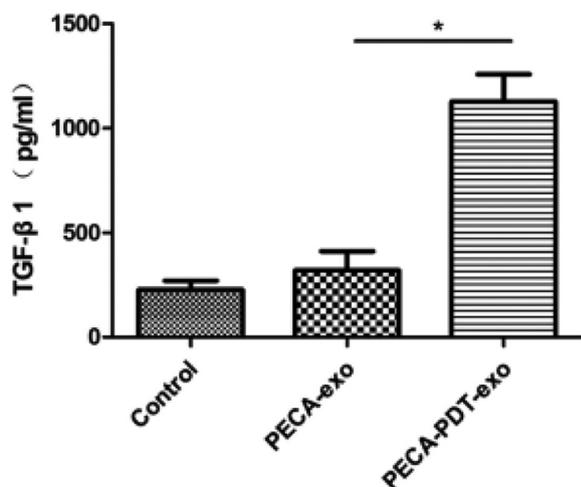


Fig. 16. – TGF- β 1 analyzed by ELISA after PDT in this study. Reproduced with permission from [53]. Copyrights 2020 Published by Elsevier B.V.

PMO load PpIX by amide bond, and this structure (PMO-PpIX) showed better tumor inhibition *in vitro* than free PpIX (Fig. 17B).

Good biocompatibility is necessary for successfully clinical application of PDT [56], and nano delivery system for PDT needs to meet this requirement as well. However, the majority types of nanomaterials are not suitable for direct *in vivo* applications due to their poor biocompatibility which would cause more damages than benefits during treatment. One of the most widely used method to improve biocompatibility of nanomaterials is to graft PEG onto their surface, as PEG is a well-recognized highly biocompatible molecule. In addition, in order to achieve efficient targeted tumor aggregation of photosensitizer by using NCs, they need to offer various pharmacological functions such as improving blood circulation and penetrating condense extracellular matrix in tumor microenvironment. One such example is reported by Chen group, where a circular aptamer-PEG system that could be activated by tumor microenvironment

was generated. Here, photosensitizer pyrochlorophyll A (PA) was first linked to aptamer, and the PA-aptamer molecules were then combined with PEG molecules to form circular PA-aptamer-PEG. The nanostructure of PA-aptamer-PEG is stable in normal physiological environment because the Schiff base bonds are stable at pH 7.4. In the acidic tumor microenvironment (pH \approx 6.5), these bonds break and smaller PA-aptamer fragments are released which are more likely to enter cells (Fig. 18) [57]. The PA-aptamer fragments in tumor cells works more efficiently under light stimulation, and aptamer could precisely label location of tumor cells for tumor imaging. Therefore, this system successfully functions as agent for both *in vivo* imaging and PDT.

Another category of new materials with PDT potential is two-dimensional materials. Among these materials, covalent organic frameworks (COFs) have attracted much attention in recent years [58]. COFs have a monolayer carbon structure similar to graphene [59], which can also contain other elements such as nitrogen and oxygen. Interestingly, porphyrins can also be integrated into COFs by Schiff base reaction or other reactions. Chen group have reported a COF-based nano PDT system using porphyrin as photosensitizer, which could treat cancer by combined photoacoustic imaging-guided photodynamic and photothermal mechanisms [60]. In this study, the photosensitizer is called COF-366 NPs, which provide the combined therapy of PTT and PDT under a single wavelength light illumination with the monitoring of photoacoustic imaging, and makes the operation simpler and more convenient. The COF-366 was synthesized by tetra (p-amino-phenyl) porphyrin (TAPP) and terephthalaldehyde using published procedure [61]. According to the authors, this COF-366 NPs as a photosensitizer could achieved good phototherapy effect even in the face of large tumors. As COF-366 can simultaneously produce both heat and ROS, it achieves highly efficient tumor suppression *in vivo* (4T1 cells were planted in mice), reaching up to 70.4% tumor volume reduction in 6 h and the temperature can reached as high as 51 °C under the 635 nm laser irradiation for 5 min (Fig. 19). This work provides an illuminating example for applying COF material and a reference for other COF-based PDT design in the future.

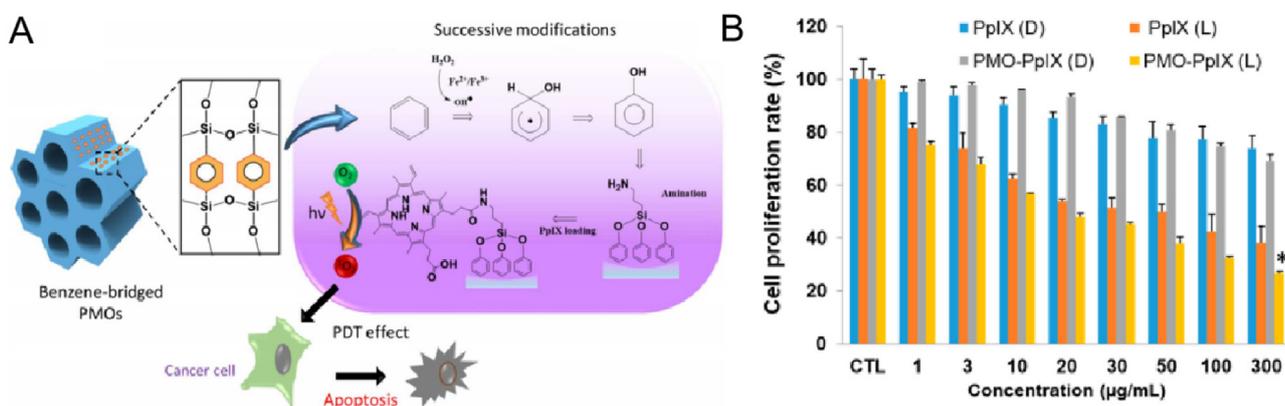


Fig. 17. – (A) Schematic of the structure for PMO skeleton, the reaction pathway of benzene hydroxylation and protoporphyrin IX (PpIX) loading, and the mechanism of photoinduced biological effects. (B) Evaluation of *in vitro* effects for PMO-PpIX in MTT. Reproduced with permission from [55]. Copyrights 2020 by the authors. Licensee MDPI, Basel, Switzerland.

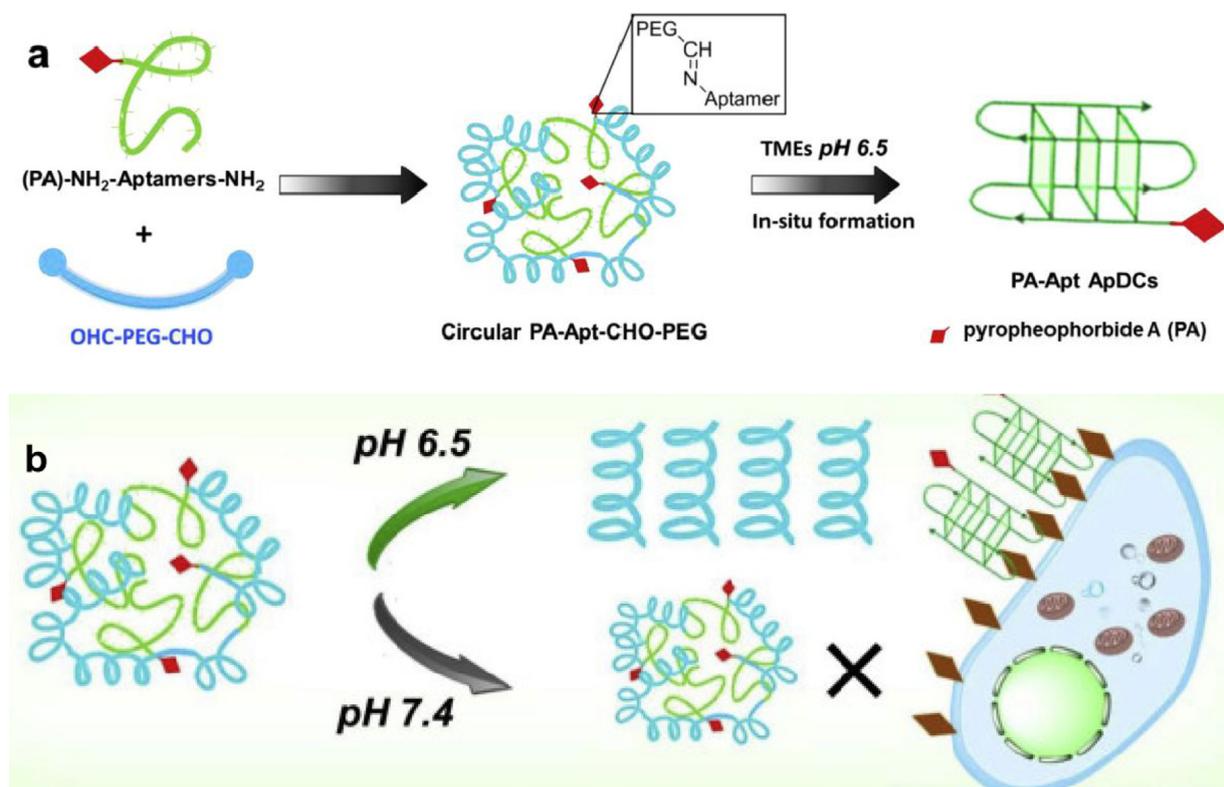


Fig. 18. – Schematic for preparation of PEG-CHO-Apt-PA, and the acid response principle in TME (pH=6.5). Reproduced with permission from [57]. Copyrights 2020 Published by Elsevier Ltd.

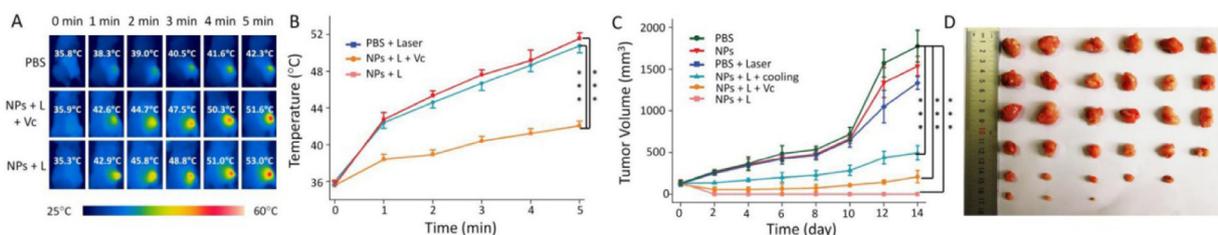


Fig. 19. – Tumor inhibition in vivo. (A, B) Temperature change of tumor site after receiving light. (C, D) Tumor volume and tumor morphology after treatment in different group. Reproduced with permission from [60]. Copyrights 2019 Elsevier Ltd.

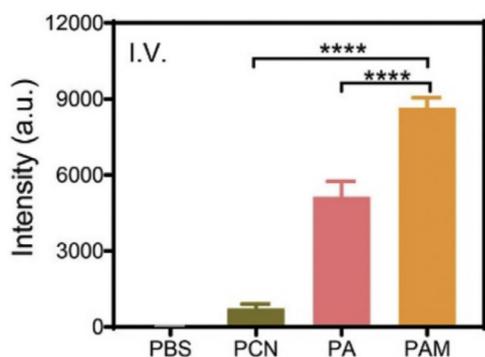


Fig. 20. – Semi-quantitative data of ROS production in vivo for different materials after intravenous illumination. Reproduced with permission from [64]. Copyrights 2020 Elsevier Ltd.

Similar to COFs, metal organic frames (MOFs) are also popular novel materials for drug delivery and other medical researches [62]. There are two main advantages for using MOFs: first, like COFs, MOFs themselves could be designed to possess pharmaceutical functions and can be further modified with various functional groups; second, MOFs can hold metal ions which are powerful tools in diseases diagnosis and treatment due to their unique physiochemical properties [63]. Because metal-based reagents are generally lack targeting ability, the target delivery potential of MOFs are critical in enhancing their performance. Zhang group has reported a MOF design which contains silver ions and could be activated by near infrared light (NIR) for tumor or infection treatments [64]. This structure was constructed by decorating silver nanoparticles (AgNPs) onto the porphyritic porous coordination network (PCN) and further camouflaging with the neutrophil membrane (NM) with inflammatory

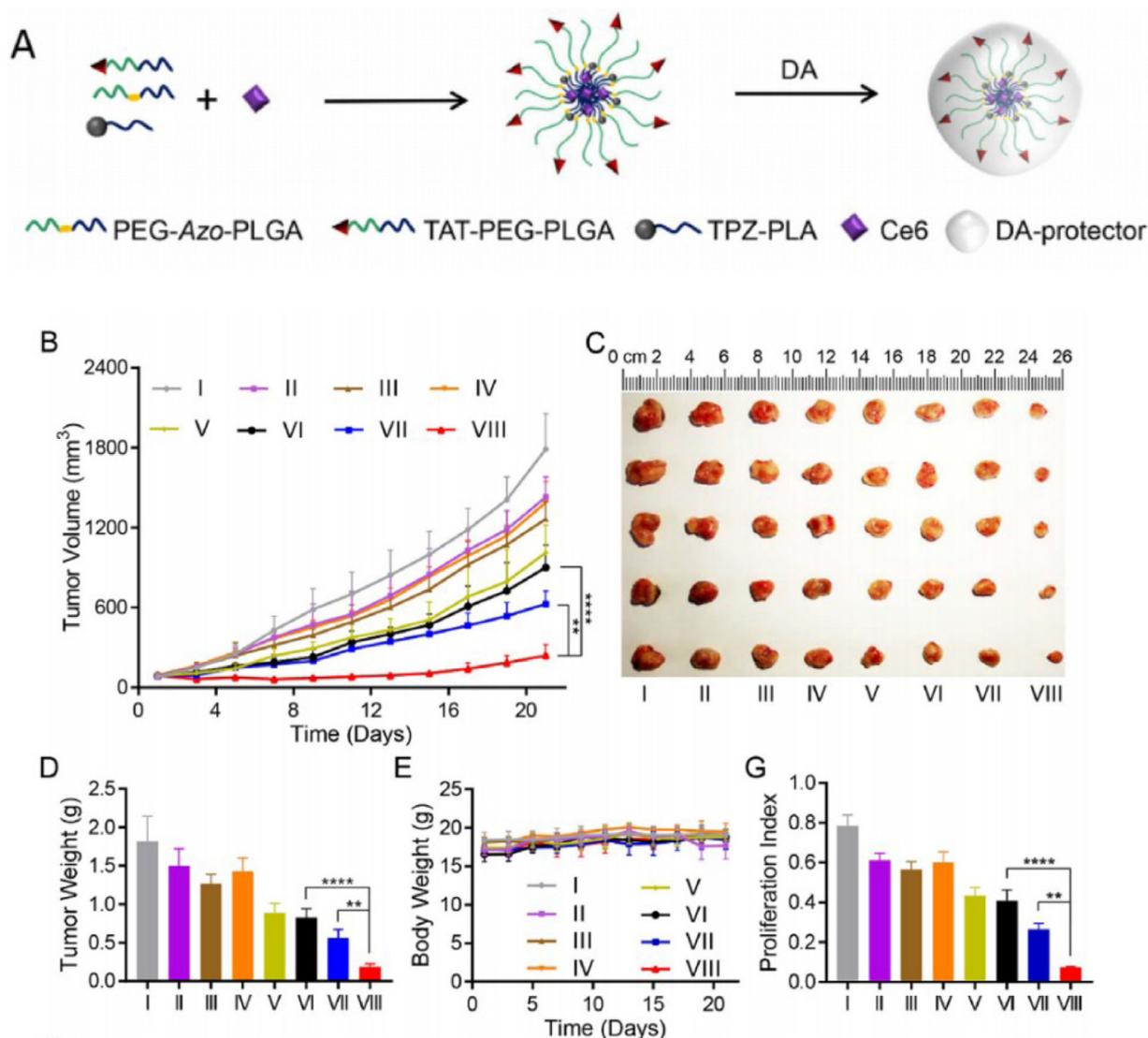


Fig. 21. – (A) the structure of the nano-drug delivery system. (B,C,D,E,G) *In vivo* efficacy of TAT+AzoNPs@ (Ce6+TPZ). (I) control group, (II) the system without light, (III) Free (Ce6+TPZ) with light, (IV) TAT+AzoNPs@ TPZ with light, (V) TAT+AzoNPs@ Ce6 with light, (VI) NPNs@(Ce6+TPZ) with light, (VII) AzoNPs@(Ce6+TPZ) with light, and (VIII) the system with light. Reproduced with permission from [65]. Copyrights 2020 Elsevier Ltd.

targeting ability (PAM). Using porphyrin as photosensitizer, NIR stimulation could produce singlet oxygen to partially degrade the MOF NPs and release cytotoxic Ag⁺ for metal ions therapy (MIT), which works together with the generated heat and ROS to kill target cells or pathogens. Results showed that PDT and MIT are mutually reinforcing in this system, as the incorporated AgNPs could also enhance the efficiency of PCN to produce ¹O₂ due to the localized electric field effect (Fig. 20).

4.2. Combining PDT with other type of therapies

Besides, PDT can also be used with other therapies to improve the overall treatment efficiency and potentially reduce adverse effects. The basic principle of PDT is energy conversion from light irradiation, which may be employed for other chemical reactions. One of the applications is light

triggered drug release system where release timing and location of chemotherapy drugs or other drugs could be precisely controlled. Jiang group reported a NC for effective synergistic bio-reductive chemotherapy using stepwise-activatable hypoxia triggered by light via photosensitizer [65]. This system include TAT (targeting peptide), chlorine e6 (photosensitizer), TPZ (hypoxia activatable prodrug tirapazamine) and PEG-Azo-PLGA (amphiphilic polymers linked by azobenzene) (Fig. 21A). Chlorine e6 (ce6) was used as the photosensitizer, which could induce hypoxia in tumor tissue under light stimulation by the releasing of TPZ. The Azo-benzene bonds in this system are stable under normal oxygen level and easy to break under hypoxic conditions. This would lead to degradation of the nanoplatform and release of loaded drugs. Hence, drug could be controlled and released at tissues experiencing light stimulation. In this

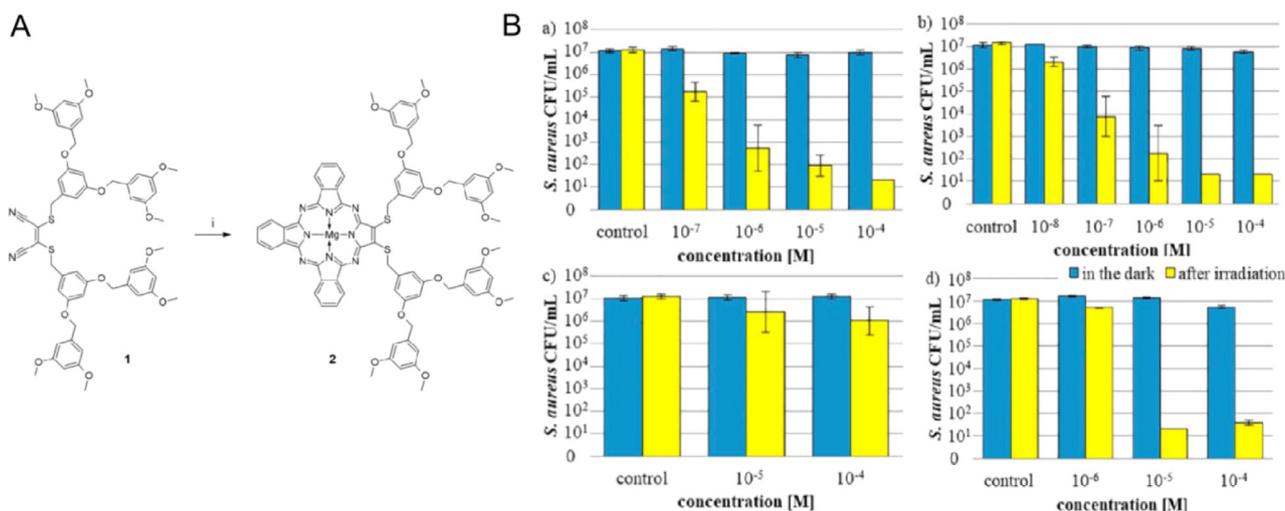


Fig. 22. – (A) Synthesis route of new tribenzo porphyrin, the synthesis steps are shown in the original text. (B) The number of viable *S. aureus* after PDT using TBP. Reproduced with permission from [67]. Copyrights 2020 Elsevier B.V.

way, tumor cells are under attack from both chemotherapy drug and PDT effects (e.g. hypoxia and heat), and damage to other normal tissues by chemotherapy could be reduced (Fig. 21B-21E and 21G). In addition to this type of application, this drug-releasing NCs can also be used in combination with other response measures (such as pH-responses) to achieve higher targeted delivery efficiency. The PDT-based drug-controlled release system thus appears to be a promising research direction.

5. PDT for non-cancer diseases and conditions

Most of reports reviewed above were aimed to treat cancer, but application of PDT is not limited to cancer treatment. Because light stimulation is highly precise and easy to apply to shallow tissues, PDT could be used to treat a wide range of skin problems. As ROS generated by photosensitizer is often very effective against microbials [66], PDT is often used for bacterial and fungi related conditions [67]. In fact, currently, far more PDT treatments are conducted for non-cancer conditions (e.g. skin fungus infection) than cancer, partially attributed to the fact that many PDT treatment of skin problems does not need injection of PDT agent into tissues or blood vessels. Due to the high occurrence of skin-related conditions and other surface disinfection applications, it is important, and probably easier for clinical translation, to develop new PDT systems for non-cancer conditions. Therefore, it is worth mentioning some examples of PDT designed for these applications.

The team of Tomasz Goslinski reported a PDT system using tribenzoporphyrines (a type of porphyrine) with dendrimeric peripheral substituents as the photosensitizers for treating *Staphylococcus aureus* (*S. aureus*) infections (Fig. 22A). This photosensitizer displayed high killing efficiency against *S. aureus* (and potentially other Gram-positive bacteria), with log reductions of *S. aureus* number at 4–5 with very low concentration ($\sim 10^{-6}$ M) and 660 nm light exposure for 20 min (Fig. 22B). Besides, it also showed improved bacteria

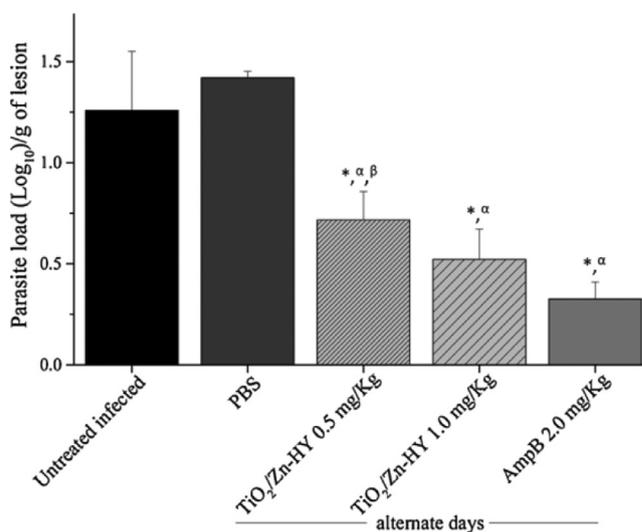


Fig. 23. – Parasite load of mice infected with *Amazon L. amazonensis* treated with TiO_2/Zn in PDT. Reproduced with permission from [68]. Copyrights 2020 Elsevier B.V.

cell wall permeability, hence this simple PDT system warrants further investigation.

A study of Graminha group has designed an inorganic photosensitizer complex which uses TiO_2 NPs doped with Zn and hypericin ($\text{TiO}_2/\text{Zn-HY}$) to treat cutaneous leishmaniasis caused by parasite *Leishmania amazonensis* (*L. amazonensis*). $\text{TiO}_2/\text{Zn-HY}$ showed good anti leishmanial activity and low cytotoxicity against murine macrophage in visible light *in vitro* [68]. Under 22 mW/cm² intensity and 52.8 J/cm² fluency delivered blue and red light, the parasite level of *L. amazonensis* in infected BALB/c mice have decreased to 43%–58% of original level (Fig. 23). This study shows the potential of PDT in parasite treatment and provides a good inorganic photosensitizer candidate for further research.

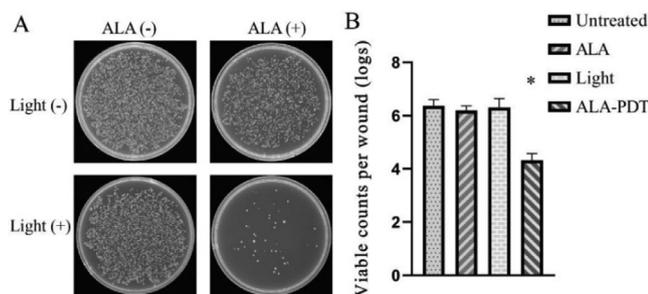


Fig. 24. – Analysis of viable bacteria count after PDT treatment. Reproduced with permission from [71]. Copyrights 2020 Elsevier B.V.

Human papillomavirus (HPV) infection is a common cause of skin problems, including vulvar intraepithelial neoplasia. Curcumin is a nature bioactive compound with antineoplastic properties [69]. Rahal et al. has devised a nano emulsion of curcumin (NE-CUR) which enhances performance of curcumin in PDT against vulvar intraepithelial neoplasia induced by HPV. In this study, they have observed that about 90% of death cell were under the irradiated in the presence with NE-CUR [70]. This result suggested that this nano emulsion has attained good biocompatibility, and the large amounts of cell death occur only when exposed to light. As the authors state, this drug delivery system in PDT may become promising in treatment of HPV infection.

The porphyrin precursor 5-ALA has also been reported for treating conditions caused by drug-resistant bacteria infection such as methicillin-resistant *S. aureus* (MRSA). MRSA can cause serious infections in diabetic ulceration and common antibiotics are ineffective in treating such infections [71]. Wang et al. reported an effective 5-ALA based PDT system to treat MRSA infected wounds of diabetic mice. In the study, 5-ALA was made into a 10% solution and placed into the wounds which were infected with MRSA, and use 635 nm light was used as the irradiation source. Since PDT kills bacteria with a mechanism that is different from antibiotics, comparing with antibiotics methicillin, 5-ALA could effectively inhibit the growth of MRSA and treat related condition caused by MRSA infection (Fig. 24). The results indicate that ALA-PDT may become a potential treatment option for MRSA-infected diabetic wounds.

For the same reasons, PDT also has the potential to treat other infections by drug-resistant bacteria. A clinical report of Florence Institute of Superior Teaching describes a case of palatal ulcer that is not sensitive to antibiotics but responds well to PDT and photobioregulation therapy (PBMT) [72]. The results show that the combination of PDT and PBMT were able to enhance and accelerate the healing process and reduce the number of bacteria. This finding provides further evidence supporting the application of PDT for treating drug-resistant infections that are difficult to be managed by other traditional treatments.

In addition to bacterial infections, PDT can also be used to treat certain autoimmune diseases that are otherwise difficult to treat. Alopecia areata (AA) is a complex immune-mediated

disorder, which has a high relapse rate with traditional treatment options. PDT combined with traditional therapy, like injection of drugs with microneedles (MN), may achieve better therapeutic effect. In a clinical trial involving 41 AA patients, 41 AA patients were divided into 3 groups, and groups of patients were treated with different treatments (only by MN, only by PDT, and PDT+MN). Most of the patients treated with this PDT approach showed reduced severity of their symptoms. Experiments showed that using MN administrated PDT with 5-ALA photosensitizer resulted in high competence against AA by effectively suppressing related immune reaction, which is likely due to precise local administration of therapeutic agents through skin by MN [73]. This study suggests that the combination of ALA-PDT with MN could be an alternative therapeutic option in the treatment of AA.

6. Discussion and conclusion

Due to its unique activation mechanism, PDT is highly effective at local stimulated areas, and could be non-active or only having limited activity in unstimulated regions. However, PDT agents normally have poor targeting capability (especially for penetrating deeper in tumors) and may cause damage if staying in certain tissues for too long. There are different ways to solve this problem. Apparently, developing new photosensitizers with significantly higher efficiency and better biocompatibility is the most direct solution. Unfortunately, completely new design which meets these demands is difficult to create. We have reviewed some recently reported novel photosensitizers, both inorganic and organic. These agents may not be ideal, but all have their advantages, hence could still provide useful reference for future photosensitizer design.

There are also other less direct ways to improve PDT effectiveness. One such way is supplementing targeting ability to PDT agents by using drug delivery system, which could enhance local PDT agent accumulation and reduce damage to normal tissues. On the other hand, plenty of combined therapies using PDT together with the likes of radiotherapy and chemotherapy are developed in order to improve the overall therapeutic effect. Yet another strategy is to use PDT agents as a switch for drug delivery systems, where PDT agents play dual roles. This is usually achieved by using active by-product of PDT (e.g. ROS and singlet oxygen) to induce designed chemical reactions, such as the breaking of certain bonds. All these different strategies are covered in this review. They offered examples for achieving different purposes and probably emphasizing on different aspects, with some provided higher overall anti-tumor effects, some displayed better biodistribution and pharmacodynamics, some designed simpler preparation processes, etc. It appears that, for inorganic photosensitizers, many researches focused on granting more function to the photosensitizers themselves; and for organic photosensitizers, main interest is to increase their local concentration, often relying on nano delivery vehicles. Combined therapies were explored for both types of photosensitizers, and provided some promising results.

In summary, PDT as an unique light-targeted therapy has high research and practical value, both owing to its therapeutic advantages and its mechanism. This review provides an brief introduction to PDT, focusing on photosensitizers which are the core of a PDT system. We covered most of the areas of current photodynamic research and clinical application. From the included research articles in this review, it is clear that PDT has the capability to be used in wider applications and there are still plenty of room for improved performance and lower toxicity for PDT. Many possibilities are still unexplored in this field and the directions investigated by the included studies are valuable clues for future research which could produce fruitful results. With the development and application of various effective and low biotoxicity photosensitizers and related delivery systems, the PDT could become an indispensable tool for the improvement of human health.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2020.12.003.

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