


# Strategies to Improve Photodynamic Therapy Efficacy of Metal-Free Semiconducting Conjugated Polymers

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**Abstract:** Photodynamic therapy (PDT) is a noninvasive therapy for cancer and bacterial infection. Metal-free semiconducting conjugated polymers (SCP<sub>s</sub>) with good stability and optical and electrical properties are promising photosensitizers (PSs) for PDT compared with traditional small-molecule PSs. This review analyzes the latest progress of strategies to improve PDT effect of linear, planar, and three-dimensional SCP<sub>s</sub>, including improving solubility, adjusting conjugated structure, enhancing PS-doped SCPs, and combining therapies. Moreover, the current issues, such as hypoxia, low penetration, targeting and biosafety of SCP<sub>s</sub>, and corresponding strategies, are discussed. Furthermore, the challenges and potential opportunities on further improvement of PDT for SCPs are presented.

**Keywords:** semiconducting conjugated polymers, photosensitizer, photodynamic therapy, enhancing phototherapy strategies

## Introduction

Photodynamic therapy (PDT) is a noninvasive treatment method that can prevent several side effects of chemotherapy and radiotherapy. PDT interferes with the balance between reactive oxygen species (ROS) generation and detoxification by selecting the appropriate wavelength of light-activated PSs and destroys the components of cancer cells. Traditional photosensitizers (PSs) are small organic molecules that usually have short excitation wavelength, low structural stability, and poor solubility.<sup>1</sup> Therefore, SCP<sub>s</sub> with light-harvesting capability to absorb visible light and near-infrared (NIR) and efficient energy transfer due to its delocalized p-system<sup>2-4</sup> have been actively developed. SCP<sub>s</sub> have a conjugated structure and high stability, and its boundary contains hydrophilic groups, which has good biocompatibility<sup>5</sup> and essentially prevents the toxic side effects of heavy metal ions and small molecules on the organism compared with inorganic semiconductors TiO<sub>2</sub>,<sup>6</sup> ZnSe/ZnS,<sup>7</sup> and CdSe.<sup>8</sup> These properties promote the application of SCP<sub>s</sub> in the biomedical field, such as fluorescence imaging,<sup>9-11</sup> PDT,<sup>12,13</sup> photothermal therapy (PTT),<sup>14,15</sup> and antibacterial application.<sup>16,17</sup>

## Brief History of PDT Based on SCP<sub>s</sub>

The groundbreaking report on conjugated polymer PDT can be traced back to the study by Ikada in 1997. Under light irradiation, PEG-fullerene C<sub>60</sub> may successfully create singlet oxygen (<sup>1</sup>O<sub>2</sub>).<sup>18</sup> However, fullerene has low solubility and activity, resulting in

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the delayed development of SCPs for PDT. Carbon-based nanomaterials, such as graphene quantum dots (GQDs) and graphitic carbon nitride (g-C<sub>3</sub>N<sub>4</sub>), have the advantages of chemical inertness, ease of operation, high photostability, and good biocompatibility.<sup>19–22</sup> These materials' electronic bands are analogous to conductive metals, and their chemical composition and electronic structure are highly adjustable.<sup>23</sup> In the last 10 years, many types of SCPs have emerged, such as polypyrrole,<sup>24</sup> polythiophene,<sup>25</sup> poly(cyclopentadithiophene, benzothiadiazole),<sup>26</sup> polyfluorene,<sup>27</sup> porphyrin-based covalent organic framework (COF).<sup>28</sup> The historical development of SCPs in PDT is shown in Figure 1.

### Basic Principle of SCPs in PDT

Generally, PSs in the ground singlet state (S<sub>0</sub>) can be excited to the first excited singlet state (S<sub>1</sub>) under light irradiation and then go through the intersystem crossing (ISC) to reach the first excited triplet state (T<sub>1</sub>). PSs at T<sub>1</sub> can directly interact with the substrate to generate ROS and induce tumor tissue destruction through apoptosis or necrosis, vascular injury, and inflammation-mediated immune response.

Based on photophysics and photochemistry, PDT can be divided into type I and II PDT (Figure 2A).

For type I PDT, electron transfer or hydrogen abstraction between PSs and substrate generate short-lived free radicals, which then immediately react with molecules, such as water and oxygen, to generate hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide radical (O<sub>2</sub><sup>•-</sup>), and hydroxyl radical (•OH).<sup>1,29</sup> SCPs with denser orbits show the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) levels. HOMO and LUMO represent the valence band maximum and conduction band minimum, respectively, of inorganic semiconductors (Figure 2B).<sup>30</sup> The release of ROS (O<sub>2</sub><sup>•-</sup>, •OH) from water by SCPs involves two parallel reactions: reduction reaction and oxidation reaction. First, the incident light energy is greater than the bandgap of SCPs, which can be excited. Second, the lower edge of the conduction band (E<sub>C</sub>) and upper edge of the valence band (E<sub>V</sub>) of SCPs represent the ability of reduction and oxidation, respectively. For example, the redox potential of O<sub>2</sub>/O<sub>2</sub><sup>•-</sup> is -0.33 V at pH 7, and SCPs (E<sub>C</sub> < -0.33 eV) can bring electrons to O<sub>2</sub>, resulting in O<sub>2</sub><sup>•-</sup> formation.<sup>31</sup> If hydrogen is extracted from water to

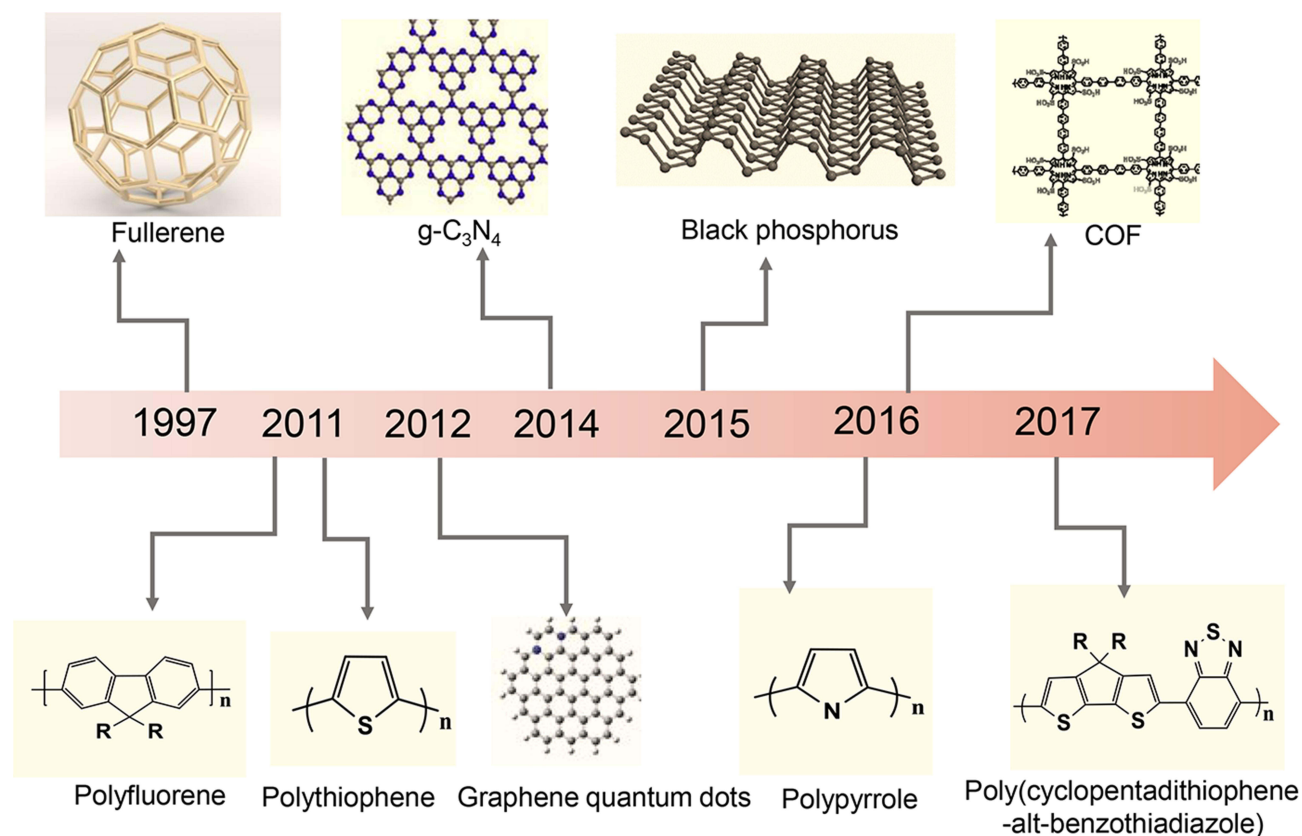
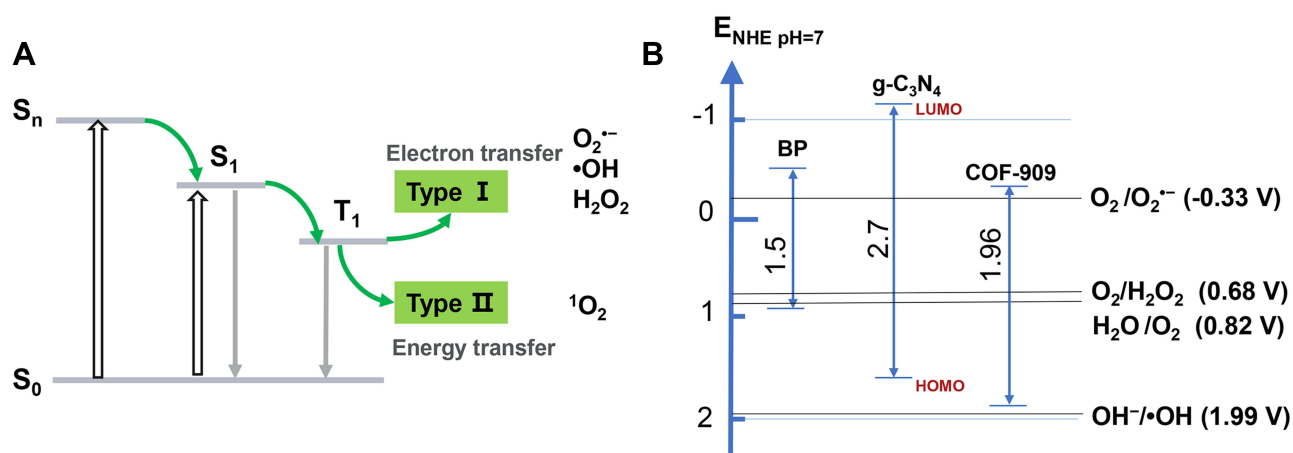


Figure 1 Timeline of SCPs for PDT.



**Figure 2** (A) Schematic illustration of SCPs photophysical and photochemical basis of PDT. (B) Reduction potential diagram of reactive oxygen species.

form hydroxyl radicals,  $E_V > 1.99$  eV are required because the redox potential of  $H_2O/\cdot OH$  at pH 7 is 1.99 V.<sup>31</sup> If  $E_V$  is  $> 0.82$  eV and the redox potential of  $H_2O/O_2$  is 0.82 V at pH 7,<sup>32</sup>  $O_2$  will be generated, which makes up for the lack of hypoxia in the tumor microenvironment. The bandgap of SCPs is 0.85–2.90 eV (Table 1),<sup>33–44</sup> when changing the type and content of monomers. To drive both  $O_2^{\cdot-}$  and  $\cdot OH$  generation, the bandgap of SCPs is at least equal to the electrochemical potential ( $\sim 2.22$  eV). However, its tissue penetrability is only a few hundred microns. Reducing the bandgap can redshift the absorption edge and increase the light absorption in NIR to improve the

tissue penetration. However, narrow bandgap means that  $O_2^{\cdot-}$  and  $\cdot OH$  cannot be obtained simultaneously. Therefore, for type I PDT, many researchers only satisfy one type of  $O_2^{\cdot-}$ ,  $\cdot OH$ , or enhance the type II PDT process to increase the yield of  $^1O_2$ . Type II PDT is energy transfer from PSs at  $T_1$  to triplet oxygen ( $^3O_2$ ), resulting in cytotoxic singlet oxygen  $^1O_2$ .<sup>45</sup> The energy band between  $^1O_2$  and  $^3O_2$  is approximately 0.96 eV, indicating that type II PDT could use longer wavelength light.<sup>1</sup> The activity of ROS is  $\cdot OH > ^1O_2$ , which can cause extensive destruction of DNA chains, proteins, and cell membranes,<sup>46</sup> while  $^1O_2$  has higher reactivity to electron-rich acceptors of C=C, indole, and aromatic heterocycles.<sup>47</sup>

**Table 1** Bandgap of SCPs

SCP <sub>s</sub>	Bandgap (eV)	Reference
Polyaniline	2.90	[33]
Polythiophene	2.10	[34]
Ladder-type polythiophene	1.50–1.60	[34]
Polystyrene pyridine copolymer	2.00–2.55	[35]
Polystyrene Pyridine thiophene terpolymer	1.95–2.31	[35]
Fluorene-based copolymers	1.95–2.00	[36]
Poly(4,7-dithien-2-yl-2,1,3-benzothiadiazole)	1.10	[37]
Polypyridine	2.06	[38]
Polypyrrole	2.33–2.39	[39]
Polyacetylene	1.35	[40]
Fullerene	0.85–1.24	[41]
Black phosphorus	0.30–2.00	[42]
$g-C_3N_4$	2.70	[43]
Porphyrin-based COF	1.60	[44]

**Abbreviations:** COF, covalent organic framework; SCP, semiconducting conjugated polymers.

This review summarizes the latest strategies of SCPs, which can overcome the tumor-associated barriers for significantly enhanced efficiency of PDT. First, we highlight the techniques to improve PDT effect of linear SCPs by improving solubility, adjusting conjugated structure, enhancing PS-doped SCPs, and combining therapies. Next, planar and three-dimensional (3D) SCPs are outlined briefly. Meanwhile, the current issues, such as hypoxia, low penetration, targeting and biosafety of SCPs, and corresponding strategies, are summarized. Furthermore, the challenges and prospects for SCPs are also discussed. We hope this review sheds light on the development of PDT to accelerate the clinical translation of SCPs.

## Linear SCPs

Linear SCP is mainly composed of  $\pi$ -conjugated main chains and has unique conductive and photophysical properties due to its extended conjugation and configurable side chain, such as large absorption cross-

section, excellent fluorescence brightness, excellent photostability and high emission rate, and low toxicity. Linear SCPs, including polythiophene, polyfluorene, and polyphenylene vinylene, have attracted considerable interest of researchers. However, due to the relatively low photosensitive efficiency of these polymers, some methods, such as improving the solubility of linear polymers, adjusting the conjugated structure of polymers, extending the length of conjugated main chain, designing D-A structure, enhancing PS-doped linear SCPs, and combining therapies, are discussed for enhanced PDT.

## Improving Water Solubility of Linear SCPs

Water-soluble SCPs can be obtained by introducing cationic anions or other polar groups, which has excellent light capture ability and high fluorescence quantum yield. In 2011, Liu and Wang et al first explored the anticancer activity of polythiophene.<sup>25</sup> Polythiophene P1 was used for PDT (Figure 3).<sup>12</sup> However, polythiophene is a hydrophobic SCP with poor water solubility and poor biocompatibility in Schanze et al introduced cation imidazole P2 to improve water solubility and broaden the visible light absorption.<sup>48</sup> Gary Bobo prepared amphiphilic cationic phosphine-based polythiophene P3.<sup>49</sup> Moreover, Zhang prepared water-soluble P4 with high <sup>1</sup>O<sub>2</sub> quantum yield (42%), photostability and pH stability.<sup>50</sup> Based on P4, Zhang shortened the hydrophobic carbon chain and prepared pure water-soluble P5 for enhanced PDT.<sup>10</sup> Liu synthesized a cationic water-soluble P6 with a quantum yield of 78%.<sup>51</sup> P6 entered the cells by hydrophobic interaction and by  $\pi$ - $\pi$  stacking and formed loose aggregates. Then, sulfhydryl groups are oxidized by high H<sub>2</sub>O<sub>2</sub> levels in cancer cells to form disulfide bonds. Moreover, Ge et al prepared highly water-dispersible P7/(DSPE-PEG 2000), which generates more <sup>1</sup>O<sub>2</sub> under the irradiation of 532 nm laser.<sup>11</sup> Xing prepared P8/polyisocyanide (PIC) hybrid hydrogel. PIC hydrogel has fiber structure and nonlinear mechanical properties and can be used as template for P8. It has higher ROS generation than P8 under red light and has good thermal reversibility and biocompatibility.<sup>17</sup> Therefore, introducing charged or sulfhydryl groups into the side chain of linear SCPs and combining with solubilizers can effectively enhance water solubility and biocompatibility to extend retention time in vivo and enhance PDT.

## Adjusting Conjugated Structure of Linear SCPs

The common method to enhance the efficiency of PSs is to improve the ISC from the lowest excited state (S<sub>1</sub>) to the lowest triplet state (T<sub>1</sub>).

According to the perturbation theory, the rate constant ( $k_{ISC}$ ) of ISC is given by the following formula:<sup>52</sup>

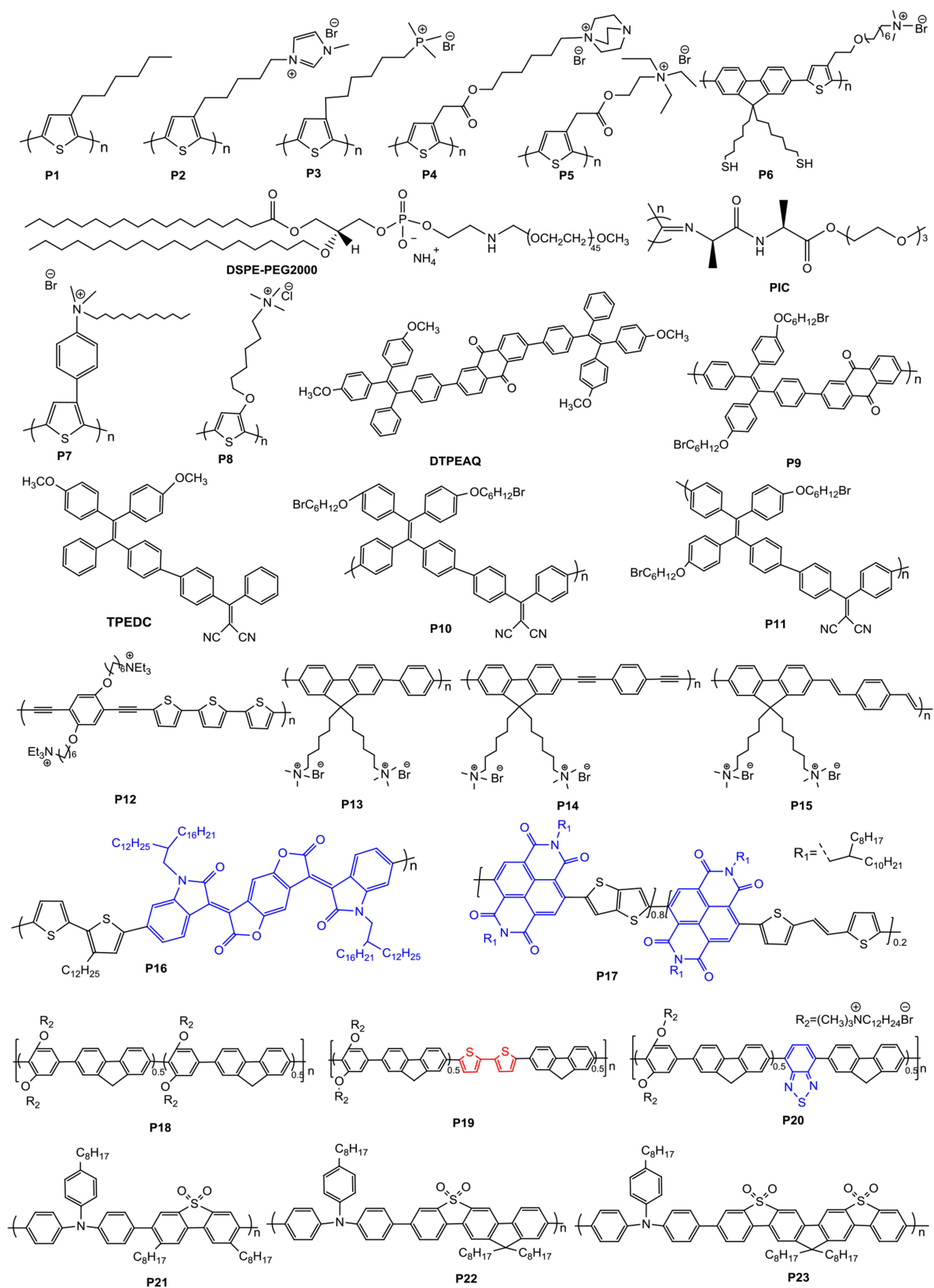
$$k_{ISC} \propto \langle {}^1\Psi | \hat{H}_{SO} | {}^3\Psi \rangle / \exp(\Delta E_{ST}^2)$$

where  $\langle {}^1\Psi | \hat{H}_{SO} | {}^3\Psi \rangle$  is the spin-orbit coupling (SOC) matrix element,  $\hat{H}_{SO}$  is the SOC Hamiltonian, and  $\Delta E_{ST}$  is the energy gap between the singlet and triplet states. According to the formula, increasing SOC matrix element can increase the  $k_{ISC}$  value. Extending SCP conjugate length<sup>53</sup> or adding heavy atoms, such as iodine,<sup>54</sup> bromide, and selenium-platinum,<sup>55</sup> into organic p-conjugated system can improve SOC and  $k_{ISC}$ . However, heavy atoms may lead to dark toxicity in biological applications. Another method is to reduce  $\Delta E_{ST}$  by designing the conjugated structure of donor (D) and acceptor (A) units.<sup>56</sup> Therefore, we will discuss the following methods of improving the efficiency of SCPs to generate more ROS for PDT.

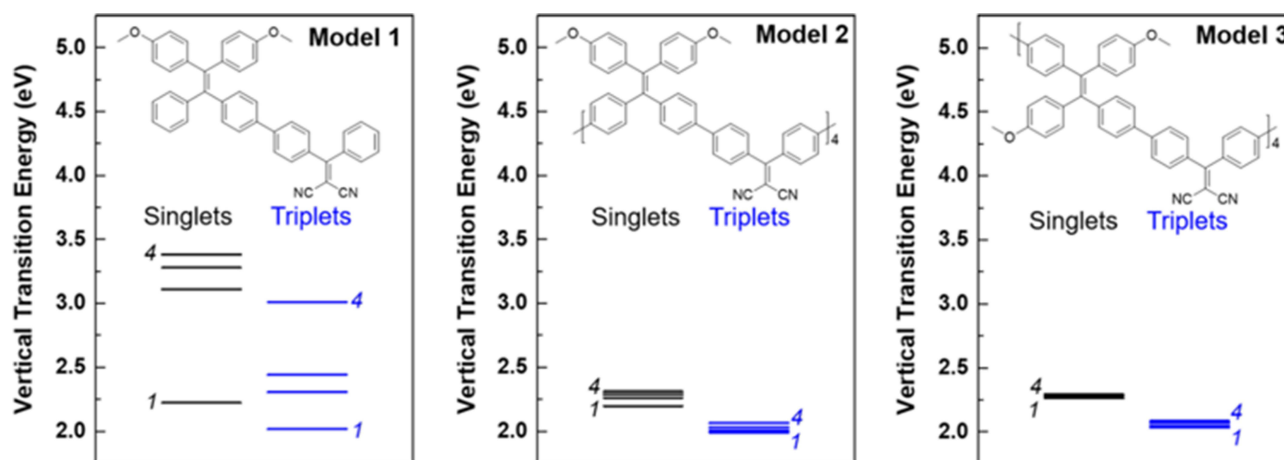
First, extending the length of conjugated main chain improve the ISC. Bazan designed oligomers and P9 with DTPEAQ as repeating unit. The <sup>1</sup>O<sub>2</sub> quantum yield of P9 is 82% and that of the oligomer DTPEAQ is only 38%.<sup>3</sup> Similarly, Liu synthesized two SCPs P10 and P11, based on the small-molecule TPEDC.<sup>57</sup> The singlet and triplet energy levels of SCPs are usually much denser than those of their small-molecule analogs, which is beneficial to <sup>1</sup>O<sub>2</sub> generation in the ISC process (Figure 4).

Based on SCPs, the conjugated length is further extended. Xu and Tan et al added a phenylene acetylene group to polythiophene main chain (P12),<sup>13</sup> which is helpful in enhancing the light trapping of polymer main chain to ensure strong fluorescence and photosensitivity. P12 can effectively generate <sup>1</sup>O<sub>2</sub> under white light, destroy lysosomal membrane and lysosomal enzyme in the cytoplasm, and promote cell death. Moreover, by introducing ethynyl and vinyl as the bridge, Xu synthesized three water-soluble P13–15. The two-photon absorption cross-section at 800 nm of P15 (ethylene bridge) was 4.5 times that of P14 (acetylene bridge) and 36 times that of P13.<sup>27</sup> Larger two-photon absorption cross-section can effectively absorb longer wavelengths and treat diseased tissues more deeply.

Second, designing the conjugated structure of donor (D) and acceptor (A) units could reduce  $\Delta E_{ST}$ . Combination of D and A into a molecule could produce



**Figure 3** Chemical structures of SCPs for PDT (electron acceptors are shown in blue; electron donors are shown in red).



**Figure 4** Chemical structures and singlet and triplet energy levels of three model compounds.

**Notes:** Reproduced with permission from: Wang S, Wu W, Manghani P, et al. Polymerization-enhanced two-photon photosensitization for precise photodynamic therapy. *ACS Nano*. 2019;13(3):3095–3105.<sup>57</sup> Copyright © 2019, American Chemical Society.

new hybridized molecular orbitals with higher HOMO level and lower LUMO level to render a small bandgap with long wavelength absorption.<sup>58</sup> Ge introduced isoindigo derivatives into the main chain of polythiophene and prepared small bandgap D-A SCPs P16. It has a significant NIR absorption peak at 782 nm and an obvious  $^1\text{O}_2$  quantum yield under NIR.<sup>59</sup> Yang synthesized a three-component P17 with low dark toxicity and high  $^1\text{O}_2$  quantum yield of 42.2% in dichloromethane solvent.<sup>60</sup> Based on “fluorene-phenylene” structural unit P18, Wang designed electron-rich thiophene P19 and electron-deficient benzothiadiazole P20 to improve optical properties. Adding electron-deficient groups to the fluorene-phenylene structure can significantly improve ROS generation.<sup>61</sup> Guo et al<sup>62</sup> synthesized P21–23 containing dibenzothiophene-S and S-dioxide derivative acceptors and introduced SO units into conjugated main chains, which had a narrower bandgap, thus enhancing the electron transport capacity.<sup>63</sup> P22 has a relatively large two-photon absorption cross-section of  $3.29 \times 10^6$  GM and good ROS generation capacity.

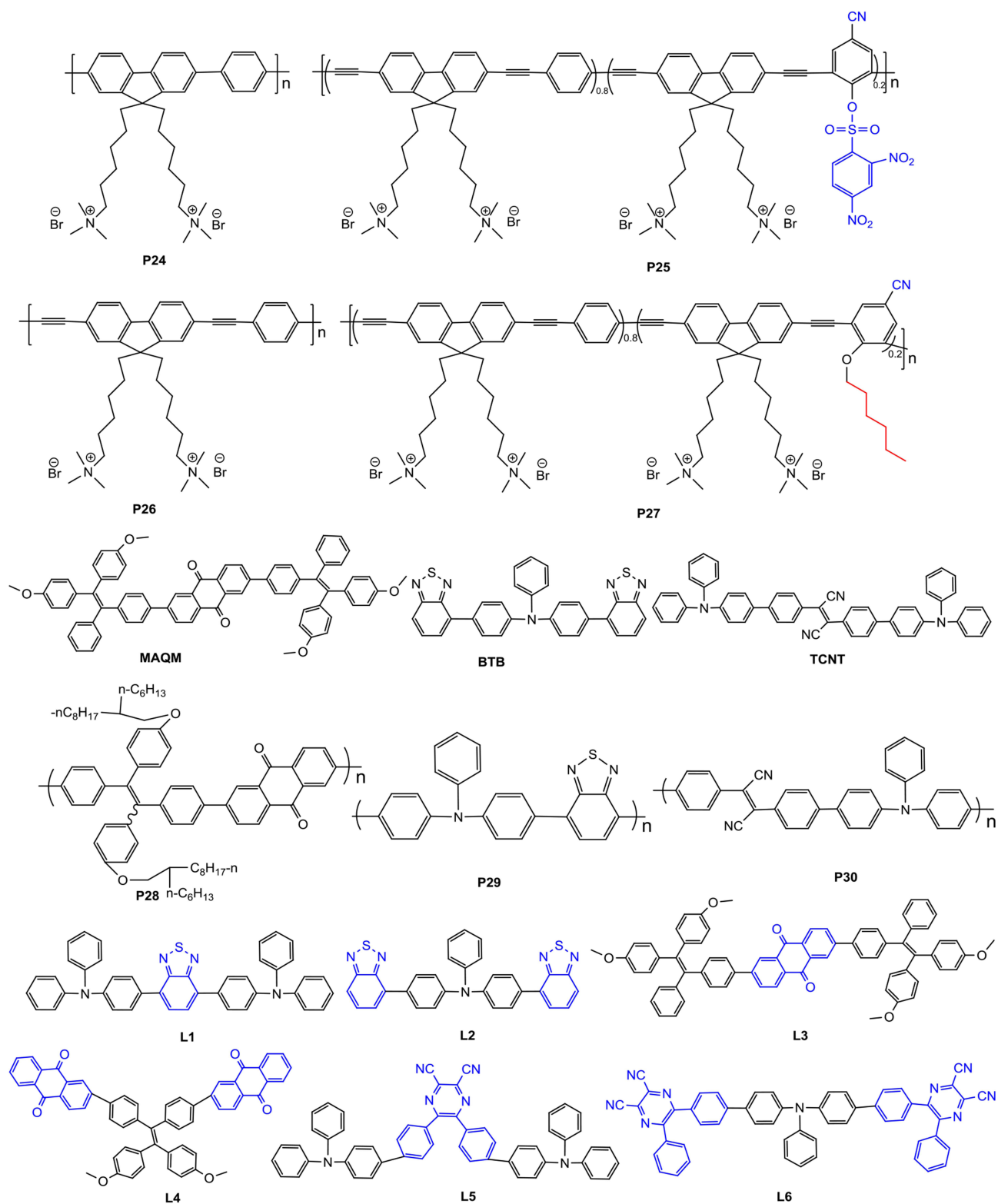
Tang et al<sup>64</sup> prepared four types of SCPs P24–27 with electron donating (red) and withdrawing groups (blue) (Figure 5). The ROS generation rate of poly(fluorene cophenylene acetylene) derivatives P25, P26, and P27 is higher than that of poly(fluorene-phenylene) derivative P24, and the D- $\pi$ -A structure is better than the A- $\pi$ -A structure. Similarly, Tang et al<sup>65</sup> designed three SCPs P28–P30 with three small molecules, BTB, TCNT, and MAQM. The results showed that SCPs have higher ROS generation efficiency than small molecules. They also

designed D-A-D and A-D-A (L1vsL2, L3vsL4, L5vsL6, blue as receptor unit). The A-D-A structure has higher photosensitive efficiency than the D-A-D structure (L1 < L2, L3 < L4, L5 < L6).

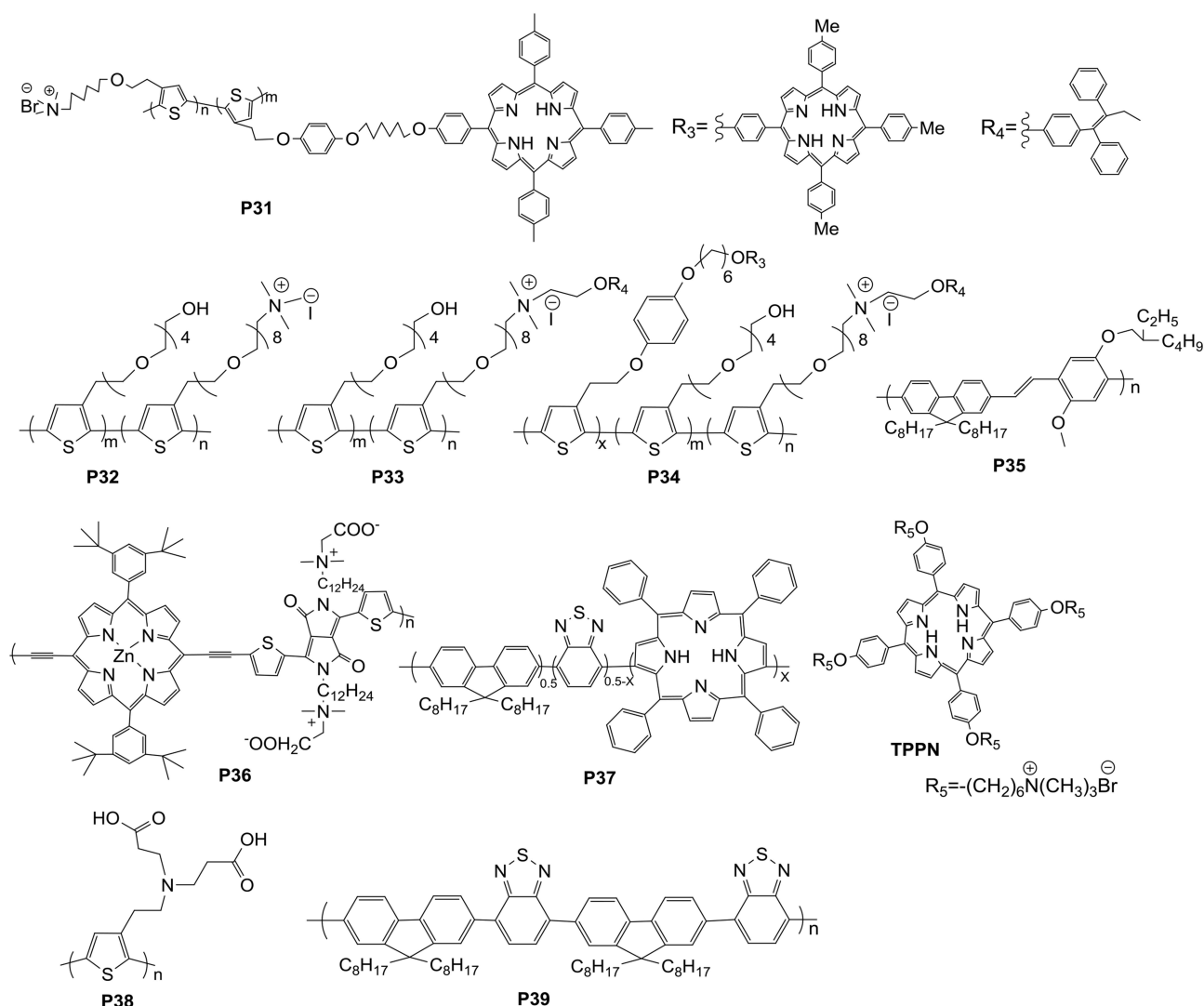
The abovementioned results show that introducing electron-withdrawing groups into the linear conjugated main chain can effectively improve ROS generation, and its performance is affected by the proportion and arrangement order of D-A units; for example, D- $\pi$ -A is superior to A- $\pi$ -A, and A-D-A is superior to D-A-D.

## PS-Doped Linear SCPs

Fluorescence resonance energy transfer (FRET) effect refers to SCPs as donor and other photosensitizers (porphyrin, isoindigo derivatives) as acceptor and excitation energy transfer from SCPs to PSs leading to ROS generation. In 2011, Liu and Wang et al reported a water-soluble P31 (Figure 6), polythiophene-containing porphyrin in the side chain.<sup>25</sup> The excitation energy transfer from polythiophene main chain to porphyrin improved ROS generation. Compared with porphyrin, the survival rate of cancer cells is significantly reduced under 470 nm irradiation. Yang et al<sup>50</sup> synthesized P33 and P34 with tamoxifen and porphyrin receptors, respectively. The MCF-7 cells viability of P33 only decreased to 60%, while that of P32 decreased to 40%. The abovementioned two studies show that the short energy transfer distance of side chain porphyrin improved the ROS generation efficiency. SCPs can also be a chemical energy receptor. Liu et al<sup>66</sup> designed P35 as donor and tetraphenyl-porphyrin as acceptor. Meanwhile, P35 is also a chemical energy receptor from  $\text{H}_2\text{O}_2$



**Figure 5** Chemical structures of SCPs (electron acceptors are shown in blue; electron donors are shown in red).



**Figure 6** Chemical structures of SCPs for PDT.

reaction. This energy transfer strategy has strong NIR chemical luminescence and good  $^1\text{O}_2$  generation capability.

Moreover, Zhang et al<sup>67</sup> added porphyrin into conjugated main chain (P36). It has the best absorbance at 700–850 nm and can generate ROS without pH effect. Wu et al<sup>68</sup> also introduced tetraphenyl-porphyrin into the main chain of P37, which not only achieved high quantum yield of  $^1\text{O}_2$  generation (35%) but also solved issues of PS leaching and low dark toxicity, effectively damaging cancer cells and inhibiting xenograft tumor. Without covalently linking porphyrins to SCPs side or main chains, Wang et al synthesized anionic water-soluble P38 and cationic porphyrin (TPPN) complexes by electrostatic interaction between anionic SCPs and cationic porphyrins.<sup>69</sup> P38 and TPPN have an effective energy

transfer. Moreover, TPPN's energy is transferred to the triplet state by ISC; then,  $^3\text{O}_2$  is sensitized to improve  $^1\text{O}_2$  generation efficiency and enhance PDT. Hydrophobic tetraphenyl-porphyrin and P39 were prepared to dense semiconductor polymer points by reprecipitation.<sup>70</sup> The energy transfer efficiency is close to 100%, resulting in approximately 50%  $^1\text{O}_2$  quantum yield.

## Hyperbranched SCPs

In addition to the traditional linear main chain structure, branched SCPs is also worth exploring. Adams and Cooper et al<sup>71</sup> prepared a series of amorphous microporous organic polymer P40 with specific surface area of  $1710\text{ m}^2\text{ g}^{-1}$  and adjusted the bandgap in the range of 1.94–2.95 eV (Figure 7). The authors only found that this polymer had good performance of photocatalytic hydrogen evolution.



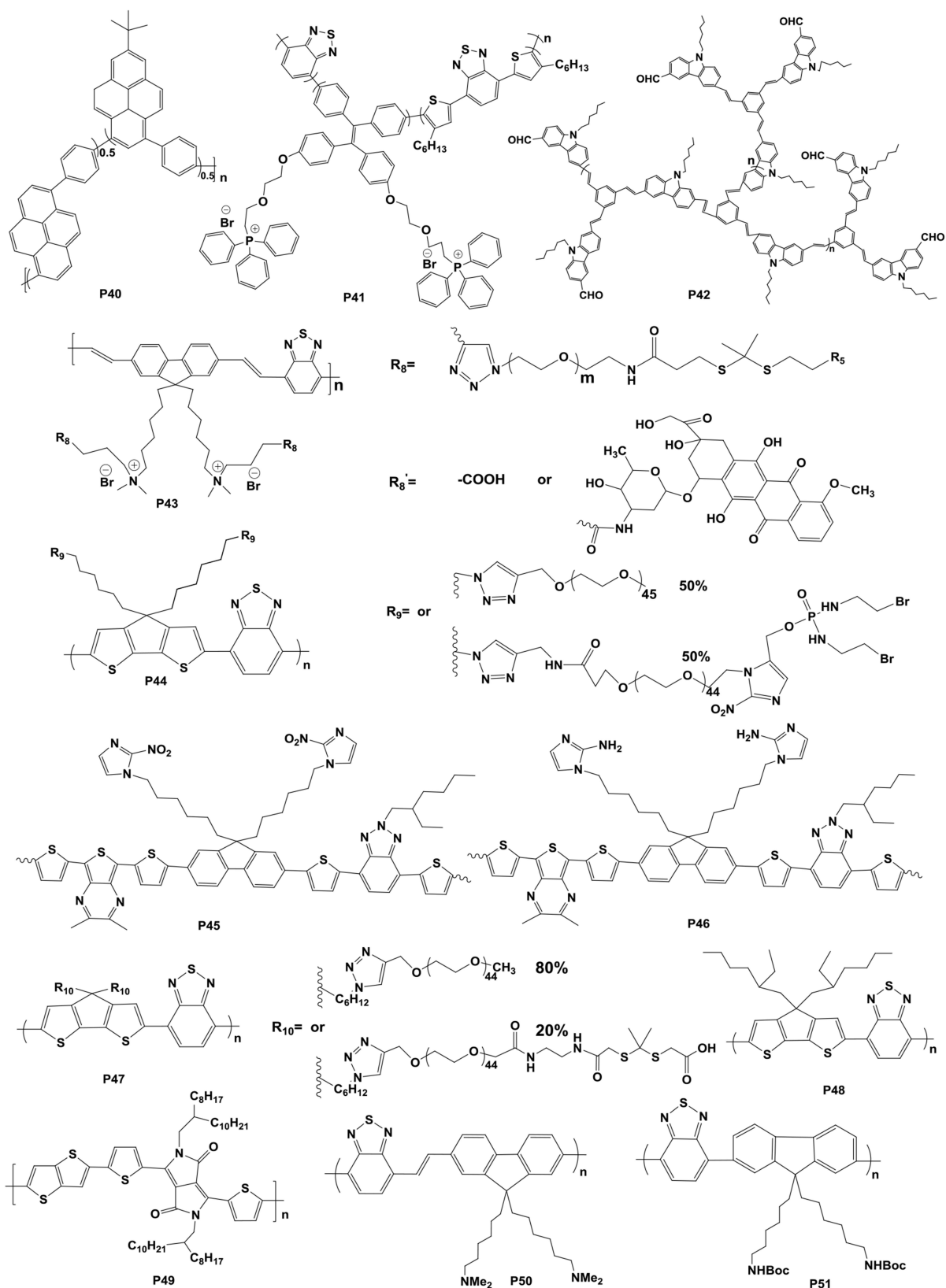


Figure 7 Chemical structures of SCPs.

The polymer with 1.94 eV bandgap can be used for PDT, but the PDT efficiency needs to be further studied. Zhou et al<sup>72</sup> reported polymer P41 with aggregation-induced emission (AIE) characteristics, red emission peak at 638–649 nm, and 25.0–30.6% fluorescence quantum yield in the aggregated state. It is suitable for PDT as a PS. Huang et al<sup>73</sup> designed a hyperbranched polymer P42. The QY in water is 27% at 800 nm. He also prepared P42/hyperbranched polyether (photothermal agent)/Ce<sub>6</sub> for two-photon excited PDT. The phase transition from the extended coil to the folded sphere shortens the distance between P42 and Ce<sub>6</sub>, which is conducive to <sup>1</sup>O<sub>2</sub> generation by FRET.

## Combined Therapies and Regulation of Drug Release by Microenvironment

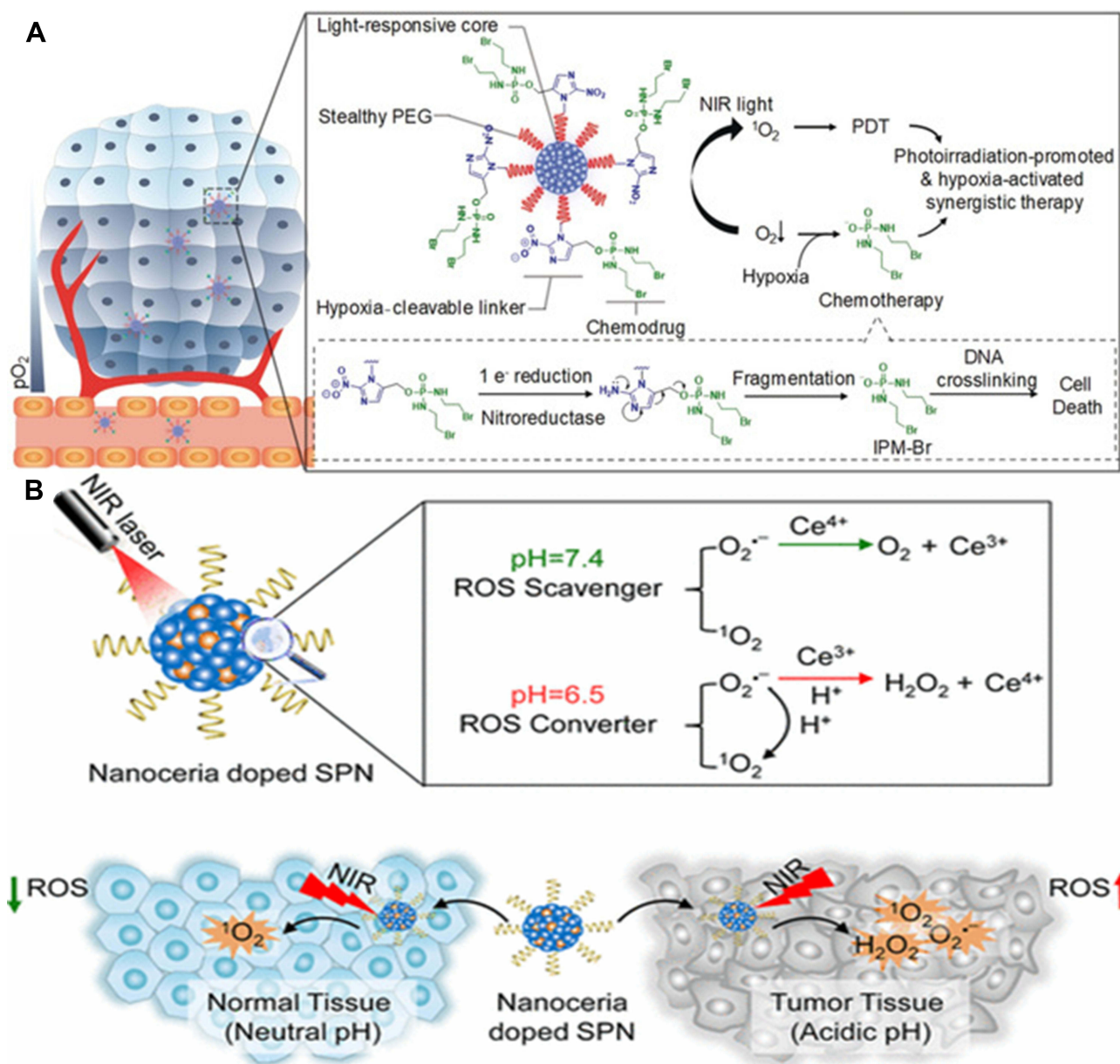
With a small radius of action (<20 nm) and short lifespan (<40 ns) for <sup>1</sup>O<sub>2</sub>,<sup>74</sup> one strategy for overcoming these limitations is combining with other therapies. To achieve the combination of PDT and chemotherapy, PSs and chemotherapeutic drugs need to be used in a drug delivery system to regulate drug release through ROS concentration, pH, and temperature in the tumor microenvironment. Liu et al<sup>75</sup> regulated the release of chemotherapeutic drugs by ROS. They combined P43 with doxorubicin (DOX) by a ROS-cleavable thioketal linker. P43 generates ROS under light, which can not only kill cells but also cut the linker at a specific location to release DOX. The results showed that the combination therapy has a stronger inhibitory effect on cell viability than single therapy. Furthermore, the release of chemotherapeutic drugs can be activated by hypoxia. Pu et al<sup>76</sup> synthesized a nanodrug system, amphiphilic P44 linked with PEG and chemotherapeutic drug isophosphatin mustard intermediate (IPM-Br) (Figure 8A). Catalyzed by nitro reductase, the hypoxia specifically initiated the cleavage and release of IPM-Br, leading to cell death. Its PDT efficiency is 18 times higher than that of the control group. Moreover, the antitumor effect is 4.3 times higher than that of P44 under NIR and hypoxia. Therefore, the combination of PDT and hypoxia-activated chemotherapy can be used in collaborative amplification of cancer therapy. Shen et al<sup>77</sup> designed a system for hypoxia activation and release of chemotherapeutic drugs. P45 was synthesized, in which dithiophenylbenzotriazole was used in ROS generation, dithiophenylpyrazine as NIR imaging agent, and 2-nitroimidazole as side chain hydrophobic component for hypoxia response transduction. The DOX was

encapsulated by double emulsion solvent evaporation/extraction and coated with polyethylene alcohol. In hypoxia, the side chain can be transformed into hydrophilic 2-aminoimidazole P46 through the single electron reduction of a series of nitroreductases and biological reducing agents (eg, abundant coenzymes in tissues), promoting the degradation of DOX/SCP nanoparticles. This SCP release system can effectively generate ROS and induce hypoxia to promote its release in cells for combined therapy.

In addition to combined chemotherapy, Pu et al<sup>78</sup> designed P47 to induce photodynamic-immuno metabolic therapy by <sup>1</sup>O<sub>2</sub>. The <sup>1</sup>O<sub>2</sub> generated from P47 can not only induce PDT but also stimulate the release of tumor-associated antigen and activate kinase, leading to loss of Kyn and increase in the proliferation and infiltration of effector T cells, improving the whole-body anticancer immunity. The researchers adjusted the ROS level according to pH conditions. Zhu and Fang et al<sup>79</sup> revealed a compound with P48 and CeO<sub>2</sub>, which can change the ROS level according to the changing microenvironment and reduce the damage to the surrounding normal tissue (Figure 8B). As a photosensitizer, P48 has strong absorption in NIR, and nanoceria can be an ROS scavenger and converter according to pH and generate less radicals under neutral condition to distinguish normal tissue and tumor and improve the therapeutic selectivity.

PDT depends on ROS but is limited by the oxygen level of the tumor microenvironment. PTT depends on the photothermal conversion of nonradioactive decay, regardless of the oxygen supply. The combination of PDT and PTT can compensate each other to improve phototherapy. For example, Yuan prepared P49.<sup>80</sup> Its temperature rose rapidly to 69.5°C in 5 min to severe photothermal cell damage under 808 nm laser irradiation. Recently, amphiphilic P3 was found to assemble with siRNA effectively, deliver siRNA targeting luciferase gene in MDA-MB-231 cancer cells expressing luciferase, and lead to 35% and 52% gene silencing effect. Meanwhile, the photodynamic activity of P3 was restored after siRNA delivery, proving their potential in the combination of PDT and gene therapy.<sup>49</sup>

Thus, improving the solubility by side chain modification could prolong the duration of efficacy in vivo. Adjusting the molecular composition of polymer could improve the electron and energy transfer in PDT and promote ROS generation. Combination with other



**Figure 8 (A)** Schematic illustration of P44 for hypoxia-activated synergistic PDT and chemotherapy. Reproduced from: Cui D, Huang J, Zhen X, Li J, Jiang Y, Pu K. A semiconducting polymer nano-prodrug for hypoxia-activated photodynamic cancer therapy. *Angew Chem Int.* 2019;58(18):5920–5924.<sup>76</sup> Copyright © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. **(B)** Schematic illustration of the self-regulated photodynamic properties of P48 at physiologically neutral, pathologically acid conditions and comparison between self-regulated and conventional. Reproduced with permission from: Zhu H, Fang Y, Miao Q, et al. Regulating near-infrared photodynamic properties of semiconducting polymer nanotheranostics for optimized cancer therapy. *ACS Nano.* 2017;11(9):8998–9009.<sup>79</sup> Copyright © 2017, American Chemical Society.

therapies improve hypoxia restriction. Therefore, the merits of SCP modification can be integrated to enhance PDT.

## Two-Dimensional (2D) SCPs

Studies show that extending the SCP size from 1D to 2D can reduce the Coulomb binding energy so that the electron hole pairs can be dissociated, thus increasing exciton dissociation yield to generate ROS. Recently, popular 2D SCPs

include g-C<sub>3</sub>N<sub>4</sub>, black phosphorus (BP), and GQDs. Many researchers reviewed the drug delivery, imaging, and phototherapy of 2D SCPs.<sup>19,20,81,82</sup> This review focuses on the modification of 2D SCPs for enhanced PDT.

### g-C<sub>3</sub>N<sub>4</sub>

Recently, g-C<sub>3</sub>N<sub>4</sub> has attracted widespread attention as PSs for PDT. It is a 2D layered SCP with inherent

semiconductor characteristics, biocompatibility, and excellent chemical stability.<sup>81</sup> The bandgap is 2.7 eV, and  $O_2^{\bullet-}$ ,  $^1O_2$ , and  $O_2$  can be generated under visible light.<sup>83</sup> Presently, the PDT bottlenecks of g-C<sub>3</sub>N<sub>4</sub> are poor tissue penetration and hypoxia. To solve these issues, researchers adjust the optical properties of g-C<sub>3</sub>N<sub>4</sub> by developing g-C<sub>3</sub>N<sub>4</sub> quantum dots (QDs), doping, and heterojunction, which allow redshift light absorption and increase NIR absorption. Then, combined with other PSs and upconversion materials, the utilization of light can be improved to maximum. Lastly, g-C<sub>3</sub>N<sub>4</sub> can be combined with chemotherapy and immunotherapy to improve the anticancer effect.

### Modification of g-C<sub>3</sub>N<sub>4</sub> Inherent Structure

First, regarding bulk size of g-C<sub>3</sub>N<sub>4</sub> and poor solubility, researchers developed g-C<sub>3</sub>N<sub>4</sub> QDs, which has good biocompatibility and small size and is beneficial in cell ingestion. Wei<sup>84</sup> prepared g-C<sub>3</sub>N<sub>4</sub> QDs (~30 nm) modified by nitrogen-rich monomer with better ROS generation. Zhang<sup>85</sup> reported low cytotoxicity and good biocompatibility of g-C<sub>3</sub>N<sub>4</sub> QDs (5 nm) an excellent PS for microwave-induced PDT. Second, the bandgap of g-C<sub>3</sub>N<sub>4</sub> is 2.7 eV and can be activated by green light, which causes low penetration depth and limits therapeutic effect to the deep tumor. Reducing bandgap by element doping could broaden NIR absorption to increase penetration depth. Xu et al<sup>86</sup> prepared 1.95 eV bandgap g-C<sub>3</sub>N<sub>5</sub>, corresponding to the absorption edge at 636 nm. The activity of g-C<sub>3</sub>N<sub>5</sub> generated  $O_2$  and  $^1O_2$  is approximately 9.5 times that of the original sample. Moreover, Cai et al<sup>87</sup> doped g-C<sub>3</sub>N<sub>4</sub> with alkali metal Zn<sup>2+</sup> and K<sup>+</sup>, its absorption edge was adjusted from 460 nm to 663 nm, and the bandgap was reduced to 1.94 eV. The ROS release rate of doped g-C<sub>3</sub>N<sub>4</sub> was approximately 45.16% (the original sample was 7.95%). Lastly, heterojunction can promote electron transfer and ROS generation.<sup>88</sup> Lu and Yang<sup>89</sup> synthesized a g-C<sub>3</sub>N<sub>4</sub>@PDA heterojunction. The absorption range of PDA can be extended from ultraviolet (UV) to NIR (660 nm). Li and Yang reported 5–10 nm gold nanoparticle (AuNP) could absorb 670 nm light energy, and excited electrons were injected into g-C<sub>3</sub>N<sub>4</sub> nanofilms, which extended the process of photoinduced charge separation and delayed the combination of electron–hole pairs to enhance type I PDT.<sup>90,91</sup>

### PS-Doped g-C<sub>3</sub>N<sub>4</sub> for PDT

PSs has a strong ability to generate ROS, but it is limited by oxygen concentration. g-C<sub>3</sub>N<sub>4</sub> can generate oxygen by water splitting. Conversely, the energy transfer of PSs and g-C<sub>3</sub>N<sub>4</sub>

can enhance PDT. Chen et al<sup>92</sup> synthesized a water-soluble, pH-activated g-C<sub>3</sub>N<sub>4</sub> nanomaterial with coupled porphyrin.  $^1O_2$  was generated by FRET between g-C<sub>3</sub>N<sub>4</sub> and porphyrin, which was highly toxic, especially in the more acidic environment of cancer cells. Similarly, Cai et al<sup>93</sup> combined g-C<sub>3</sub>N<sub>4</sub> with TMPyP4-porphyrin, which has good stability in physiological solution and selective aggregation in tumor cells. Under hypoxia, it can effectively inhibit A431 human epidermoid cancer cell growth. Cheng et al<sup>94</sup> prepared iron-doped carbon nitride (Fe-C<sub>3</sub>N<sub>4</sub>)/Ru(II) complex/hyperbranched SCP with poly(ethylene glycol). Poly(ethylene glycol) is a high two-photon collector and FRET's donor.  $O_2$  was released to compensate for oxygen consumption during PDT and promote  $^1O_2$  generation under 800 nm two-photon radiation. The multiple PSs show more effective separation of electron hole pairs and significantly higher light utilization efficiency and enhanced PDT efficiency than any single PS.

### Combined Therapy

g-C<sub>3</sub>N<sub>4</sub> is an effective chemotherapeutic drug carrier for enhancing the anticancer effect because of its high specific surface area. For the first time, Li et al<sup>95</sup> showed that g-C<sub>3</sub>N<sub>4</sub> nanosheets to be used as a carrier of pH-responsive nanodrug DOX. Chen et al<sup>96</sup> prepared g-C<sub>3</sub>N<sub>4</sub> as core and ZIF-8 with DOX as shell. Wang et al<sup>97</sup> also used melamine and phloxine B precursor polymerization to synthesize black g-C<sub>3</sub>N<sub>4</sub> with PDT and PTT effects. Black g-C<sub>3</sub>N<sub>4</sub> generated ROS after a single 808 nm laser irradiation for 5 min. After 8 min, the temperature exceeded 50°C, and mice tumor growth severely decreased. Lu et al<sup>98</sup> prepared 2D Ti<sub>3</sub>C<sub>2</sub> (photothermal agent)/g-C<sub>3</sub>N<sub>4</sub> heterostructure by the electrostatic assembly, which prolonged g-C<sub>3</sub>N<sub>4</sub> light absorption to NIR. It can produce  $O_2^{\bullet-}$  and  $\bullet OH$  under 670 nm for type I PDT and trigger water splitting to generate abundant  $O_2$  for type II PDT.

### BP

Phosphorus atoms in the same layer of BP are connected with three other phosphorus atoms by chemical bonds, and the different layers are connected by van der Waals interaction.<sup>99</sup> The bandgap of BP depends on the number of layers, ranging from 2.0 to 0.3 eV.<sup>100</sup> BP has excellent biocompatibility and strong biodegradability in vivo, indicating that BP is suitable for biomedicine. Zhang et al proved that stripped BP is an effective PS for generating  $^1O_2$  for the first time, with 0.91  $^1O_2$  quantum yield,<sup>101</sup>

which is far higher than those of other traditional PSs, such as porphyrin, phthalocyanine, and photodynamic nanomaterials.<sup>102,103</sup> Modifications of improving PDT are as follows:

### BP Quantum Dots (BPQDs)

Huang et al<sup>104</sup> first synthesized BPQDs. It has good stability in physiological medium without obvious cytotoxicity. More importantly, due to the ultra-small hydrodynamic diameter (5.4 nm), it can be rapidly excreted from the body through kidney clearance. Song et al<sup>105</sup> designed to embed Ag<sup>+</sup> into BPQD (~10 nm), and the direct bandgap of Ag<sup>+</sup>/BPQD is reduced to approximately 0.1 eV, corresponding to 1300 nm wavelength, significantly increasing optical absorption.

### PS-Doped BP for PDT

Wang et al<sup>106</sup> prepared BP nanosheets coated with a water-soluble and positively charged AIE-PS (NH<sub>2</sub>-PEG-TTPy), which not only works on the biocompatibility and physiological strength of BP nanosheets but also has solid fluorescence outflow at 672 nm and PDT capacity under 808 nm NIR laser. C<sub>60</sub> was covalently grafted onto the edge of BP nanosheets.<sup>107</sup> Photoinduced electrons from BP to C<sub>60</sub> promoted •OH generation for type I PDT, and its stability in serum, phosphate-buffered solution, and water was significantly improved. The hybridoma inhibition rate of BP-C<sub>60</sub> was the highest (88.2%) compared with that of original BP (36.6%).

### Combined Therapy

BP has an inherent photothermal effect. Lv et al<sup>108</sup> and Ren et al<sup>109</sup> prepared ultra-thin BP nanosheets (13 nm) with UCNPs. A 980 nm laser can achieve a photothermal conversion efficiency of 30.84%, which is substantially greater than traditional AuNPs (22.63%) and gold nanorods (23.33%). BP was mixed with additional photothermal agents by the researchers. BP@PDA-Ce<sub>6</sub><sup>110</sup> and BP-CuS<sup>111</sup> had photothermal conversion efficiencies of 33.2% and 62.6%, respectively. The researchers also combined BP with flaky,<sup>112</sup> biconical,<sup>113</sup> spherical,<sup>114</sup> and rod-shaped<sup>115</sup> AuNPs to enhance light absorption, <sup>1</sup>O<sub>2</sub> generation, and thermotherapy via local surface plasmon excitation resonance. PDT combined with chemotherapeutic agents such as DOX,<sup>116</sup> docetaxel,<sup>117</sup> and resveratrol<sup>118</sup> can enhance anticancer efficacy, inhibit tumor growth, and support the temperature sensitivity and controlled release of drugs. Also, PDT of BP can be combined with gene therapy and immunotherapy. Delivering human telomerase reverse transcriptase-small

interfering RNA (hTERT siRNA) is an important method of gene therapy. BP nanoparticles degrade in low pH and rich ROS environment, escape from acidic lysosomes by polyethyleneimine, and transfer and release siRNA into the cytoplasm for gene silencing therapy.<sup>119</sup> Song and Yang<sup>120</sup> loaded BP with immune adjuvant (CpG-oligodeoxynucleotides), an effective adjuvant for increasing cytokine secretion by antigen presenting cells, activating T cells, and recruiting them into tumor tissues. The addition of an immune adjuvant to BP may prevent them from being eliminated from circulation. This drug generated a high ROS level under NIR, leading to the transformation of hydrophobic ROS-sensitive poly(propylene sulfide) to hydrophilic polymer, leading to disintegration.

### GQDs

GQDs have excellent optical properties due to quantum limitation,<sup>121</sup> which can be used as PDT PSs. The transverse dimension is usually less than 10 nm<sup>122</sup> compared with traditional PSs, which has many advantages, such as good biocompatibility, high water solubility, and light stability. Surface functional groups and structural modifications have a significant impact on GQDs; hence, surface modification and structural design can improve the PDT of GQDs.

First, doping GQDs with heteroatoms N,<sup>123</sup> Cl,<sup>124</sup> F,<sup>125</sup> Eu, Ag, and Se<sup>126</sup> is an effective method, which can change its electronic density and optical properties to improve ROS generation efficiency. Second, PS-doped GQDs could enhance PDT.<sup>127</sup> Integrated Ce<sub>6</sub> into GQDs via disulfide bonds. Redox-responsive Ce<sub>6</sub>/GQDs significantly inhibited HeLa cell growth. Furthermore, GQD's combination therapy is comparable to other SCPs such as chemotherapy with DOX,<sup>128</sup> immunotherapy,<sup>129</sup> PTT<sup>130,131</sup> and numerous combined therapies, all of which have been reviewed.<sup>22,132</sup>

## Three-Dimensional (3D) SCPs Carbon Nanomaterials

Fullerene C<sub>60</sub> and its derivatives can generate ROS and have high quantum yield, which has gained the attention of researchers. Due to low solubility in aqueous solution and poor optical absorption in visible light and NIR, its application of PDT is limited. Ikeda believed that the combination of C<sub>60</sub> derivatives and solubilizers (eg, cyclodextrin, polysaccharide, lysozyme, and liposome) not only increases its water solubilization but also enhances its permeability and

retention effect. These water-soluble complexes C<sub>60</sub>-C<sub>70</sub> have high photoinduced cytotoxicity to HeLa, HaCaT, and RAW 264.7 cells under 350–500 nm light and no cytotoxicity (light >600 nm).<sup>133</sup> Moreover, to improve the hydrophilicity of C<sub>60</sub>, Lee et al<sup>134</sup> prepared a composite of C<sub>60</sub> powder and nanodiamond by simple grinding, which is a stable aqueous colloidal suspension. A part of the diamond shell carbon is oxygenated for hydrophilic property so that the complex is scattered in water and physiological media. C<sub>60</sub>-diamond causes mice tumors to shrink through rapid cell ingestion and <sup>1</sup>O<sub>2</sub> generation under visible light.

## COF

COF is a porous crystal material in which organic building blocks or elements (C, N, O, B) are connected by various covalent bonds to form 2D or 3D long-range ordered periodic structures. COF also has excellent properties<sup>135</sup> but contains heavy metal ions. COF has many advantages of free heavy metal, relative stability, good biocompatibility, strong  $\pi$  stacking conductive path, high specific surface area, and large pore volume, contributing to ROS or photon diffusion. Therefore, COF is an ideal PS candidate and shows great potential in PDT.

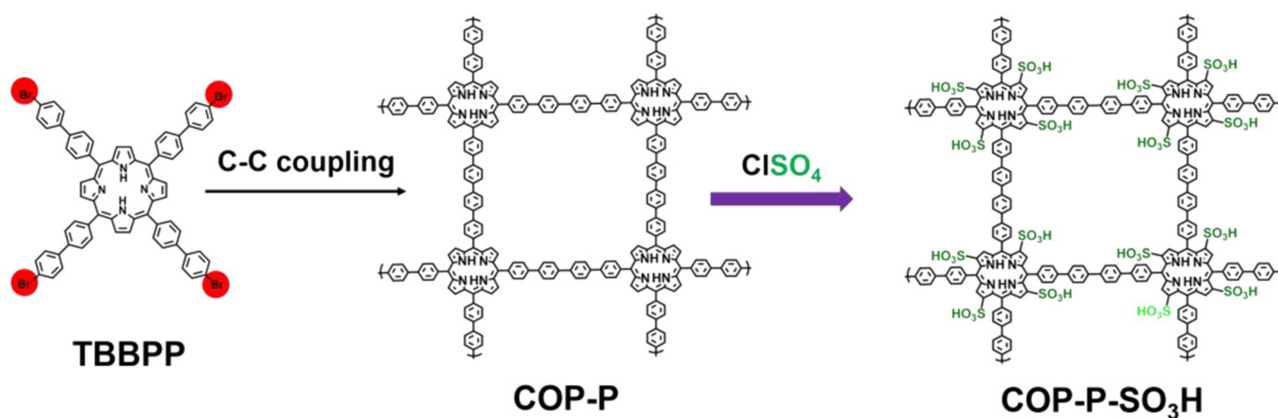
### Improving Solubility of COF

COF's biomedical application is limited due to its large size and poor colloidal stability in aqueous solution. In 2016, Chen et al applied COF to PDT for the first time. To improve COF water dispersivity, they<sup>28</sup> synthesized a completely conjugated 2D COP (COP-P-SO<sub>3</sub>H; Figure 9). Sulfonic acid group not only improves water dispersivity but also significantly reduces bandgap to enhance optical absorption and

redshift absorption edge. Moreover, it has high quantum yield of <sup>1</sup>O<sub>2</sub>, which is 1.2 times that of clinically approved PS (ie, PpIX). Liu et al<sup>136</sup> used meso-5, 10, 15, 20-four (4-hydroxybenzene) porphyrin (THPP) and perfluorosulfonic acid as connectors and then modified with carboxyl terminated polyethylene glycol (PEG5kCOOH) to prepare fluorinated nano-COP with excellent physiological stability. Even after freeze-drying treatment, there was no significant interference. Moreover, fluorinated chains of COP can effectively load O<sub>2</sub> and significantly enhance PDT. Recently, Liu et al<sup>137</sup> selected bovine serum albumin as a model protein and biocompatible and water-soluble drug adjuvant and used 5,10,15,20 tetrakis(4-aminophenyl)-21H,23H-porphyrin (TAPP) and 1,3,5-triamcinolone (TFP) as building blocks to synthesize stable COF, which had uniform morphology and good colloidal stability.

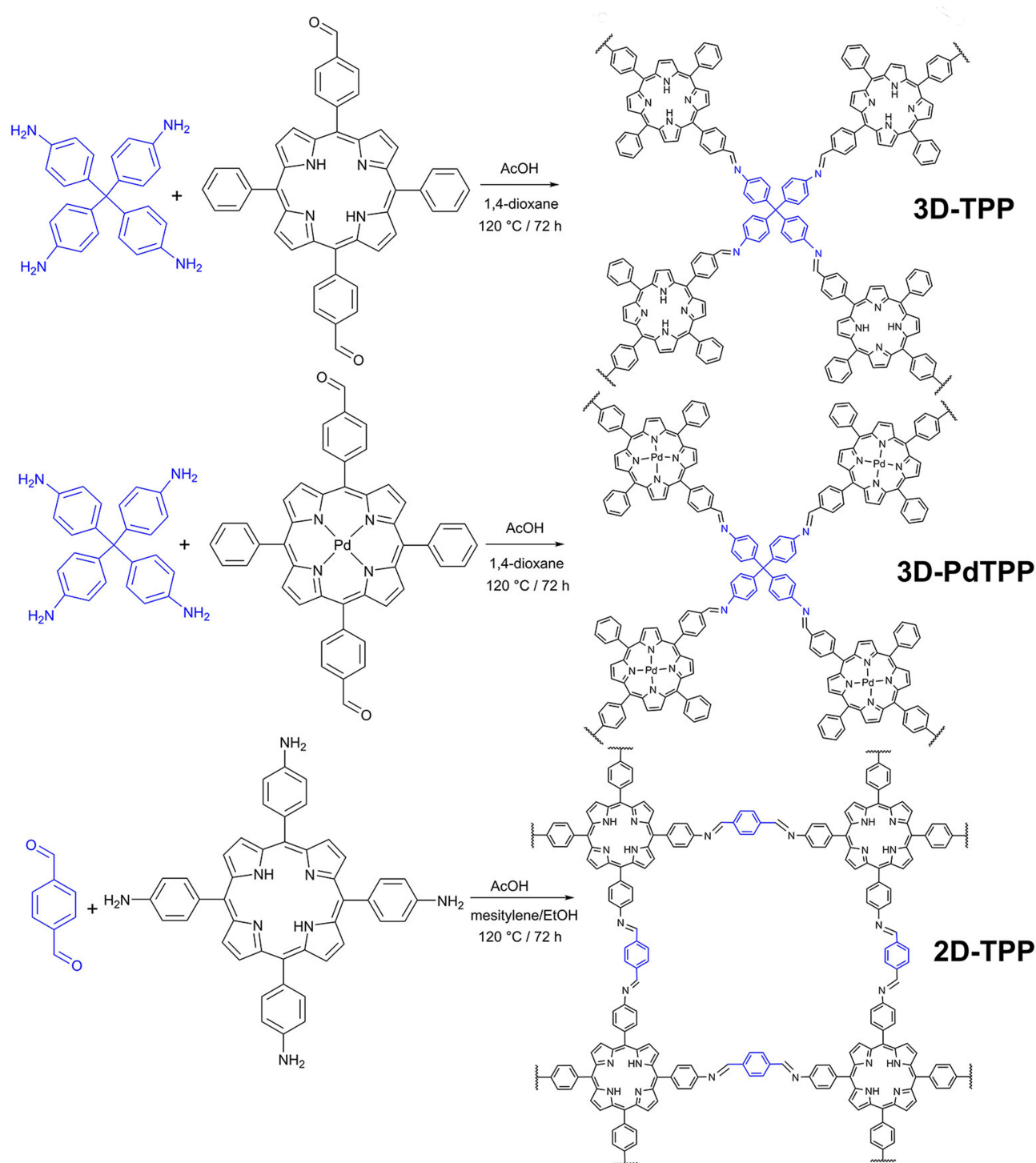
### Adjusting Molecular Unit to Expand Conjugated Structure

Lang et al<sup>138</sup> reported that sp<sup>3</sup> hybrid carbon atoms in tetraphenylmethane were connected with planar porphyrins by Schiff-base reaction to form diamond-like porphyrin-based COF (Figure 10). The photosensitive COF was not affected by the high concentration of single porphyrin unit in the structure. It has advantages of good light stability, high spectral efficiency, and good dispersibility in polystyrene. Deng et al<sup>139</sup> used molecules that cannot generate <sup>1</sup>O<sub>2</sub> by themselves to construct an expanded porous framework with high surface areas and permanent porosity. It has a 1.96 eV bandgap, which shows excellent overlap with O<sub>2</sub><sup>•-</sup>, leading to a significant improvement in type I PDT.



**Figure 9** The scheme for synthesis of COP-P-SO<sub>3</sub>H.

**Notes:** Reproduced with permission from: Xiang Z, Zhu L, Qi L, et al. Two-dimensional fully conjugated polymeric photosensitizers for advanced photodynamic therapy. *Chem Mater.* 2016;28(23):8651–8658.<sup>28</sup> Copyright © 2016, American Chemical Society.



**Figure 10** Syntheses of precursors and COFs (precursors of connection unit are shown in blue).

**Notes:** Reproduced with permission from: Hynek J, Zelenka J, Rathouský J, et al. Designing porphyrinic covalent organic frameworks for the photodynamic inactivation of bacteria. *ACS Appl Mater Interfaces*. 2018;10(10):8527–8535.<sup>138</sup> Copyright © 2018, American Chemical Society.

### PS-Doped COF

Pan et al<sup>140</sup> integrated dye-labeled oligonucleotides into porphyrin-based COF, which effectively quenched dye fluorescence through FRET. Compared with porphyrin monomer,

the large planar structure of the electron system of COF has better stability and higher ROS generation in aqueous solution under NIR irradiation. Li et al<sup>141</sup> reported BODIPY-modified nano-COFs (110 nm). Based on imino-COFs, the

free CHO (bond defect in COFs) is connected with amino substituted BODIPY by Schiff-base reaction, which is beneficial for enhancing PDT. Recently, Ca-COF-BODIPY-2I is prepared.<sup>142</sup> Covalently linked BODIPY-2I can generate  $^1\text{O}_2$  under light, and intracellular  $\text{Ca}^{2+}$  overload can lead to pro-death through synergistic effect with  $^1\text{O}_2$ .

### Combined Therapy

Porphyrin material has been widely studied for PDT, but its photothermal effect is rarely reported. Pang et al<sup>143</sup> prepared porphyrin-based covalent organic polymer by solution aging at room temperature, which has high photothermal conversion efficiency (21.7%) from 22.4°C to 57.5°C in 10 min and good PDT performance. Moreover, Pang et al prepared COF/CuSe<sup>144</sup> and COF/Ag<sub>2</sub>Se<sup>145</sup> nanocomposite, which achieved enhanced therapeutic effect through a combination of PDT and PTT.

### Hydron-Bonded Organic Frameworks (HOFs)

Liu et al<sup>146</sup> designed HOFs with large p-conjugated system and four carboxylic acid groups. They have multiple hydrogen bonds, strong P-P interaction, high chemical stability, high specific surface area of 2122 m<sup>2</sup> g<sup>-1</sup>, biocompatibility, and low cytotoxicity. Moreover, they have periodically integrating photoactive pyrene and can effectively encapsulate DOX for combined chemotherapy. Compared with MOFs and COFs, it has the advantages of mild synthesis conditions and good solution stability and can be used as excellent candidate materials for PDT.

## Issues and Strategies for Enhanced PDT

### Oxygen Reliance

Hypoxia is a typical pathological feature of almost all solid tumors and significantly reduces ROS generation. Type II PDT is limited by the oxygen concentration in the tumor microenvironment, which seriously restricts photodynamic efficacy. Furthermore, persistent hypoxia and damage to the vascular system can exacerbate hypoxia, eventually leading to failure of deep tumor therapy. Two methods are used to resolve hypoxia: reducing oxygen consumption and increasing oxygen generation.<sup>147,148</sup> For hypoxia, researchers increase oxygen supply by g-C<sub>3</sub>N<sub>4</sub> water splitting<sup>149</sup> and oxygen supply materials, such as CeO<sub>x</sub>, MnO<sub>2</sub>, and catalase, to catalyze the oxidation of H<sub>2</sub>O<sub>2</sub> to O<sub>2</sub>. Conversely, they can reduce O<sub>2</sub> consumption by targeting mitochondria and inhibiting tumor cell respiration (Table 2).

First, g-C<sub>3</sub>N<sub>4</sub> bandgap was adjusted to allow its valence band to meet the requirement of O<sub>2</sub> generation. Zhang et al<sup>149</sup> synthesized carbon point-doped g-C<sub>3</sub>N<sub>4</sub>, which enhanced its red light absorption and activated water splitting in vivo. When the O<sub>2</sub> concentration is 1%, it has a good cancer cell growth inhibition effect, improves the O<sub>2</sub> level in the tumor, and finally reverses the PDT resistance and tumor metastasis induced by hypoxia. Second, O<sub>2</sub> supply materials, such as catalase,<sup>150</sup> Fe-doped g-C<sub>3</sub>N<sub>4</sub> (similar to peroxidase),<sup>151</sup> MnO<sub>2</sub>,<sup>152</sup> and CeO<sub>x</sub><sup>153</sup> catalyze the oxidation of H<sub>2</sub>O<sub>2</sub> to O<sub>2</sub>.

Regarding BP, many artificial catalases, Pt nanoparticles,<sup>154–156</sup> FeOCl/Mn<sup>2+</sup>,<sup>157</sup> Fe-Pt NP<sup>158</sup> and AuNPs<sup>159</sup> effectively decompose the accumulated H<sub>2</sub>O<sub>2</sub>

**Table 2** Summary of Oxygen-Generating Strategies for Tumor Oxygenation

Materials	O <sub>2</sub> Generation Mechanism	Reference
g-C <sub>3</sub> N <sub>4</sub>	Water splitting	[149]
CeO <sub>x</sub>	Ce <sup>4+</sup> convert H <sub>2</sub> O <sub>2</sub> to H <sub>2</sub> O and O <sub>2</sub>	[153]
Metformin	Inhibition of the respiration of tumor cells	[153]
Catalase	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[150]
Fe-doped-C <sub>3</sub> N <sub>4</sub>	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[151]
MnO <sub>2</sub>	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[152]
Heme	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[161]
Pt-NPs	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[154,159]
Au NPs	Glucose decomposition and H <sub>2</sub> O <sub>2</sub> production	[158]
FeOCl and Mn <sup>2+</sup>	Catalytic degradation of H <sub>2</sub> O <sub>2</sub>	[156]
Fe-Pt NPs	Fe-based Fenton reaction	[157]
MOF	MOF adsorption of O <sub>2</sub>	[160]
Cyanobacteria	Photosynthesis	[162]

**Abbreviation:** MOF, metal-organic framework.



in the tumor and alleviate tumor hypoxia. Lei et al<sup>160</sup> precisely encapsulated a layer of phosphorus QDs and catalase in the inner and outer layers of MOF, respectively. The outer hydrogenase transformed H<sub>2</sub>O<sub>2</sub> into O<sub>2</sub>, then O<sub>2</sub> is directly injected into the inner BP. The PDT efficiency of the drug system is 8.7 times than that without catalase. However, excessive H<sub>2</sub>O<sub>2</sub> may lead to the off-target effect and change other normal biochemical processes. Ju et al<sup>161</sup> developed a double trigger O<sub>2</sub> self-supporting nanosystem. The BP was functionalized with a blocker DNA duplex of 50Cy5-aptamer-heme/30-heme labeled oligonucleotides. It could produce heme-dimer used to inactivate peroxidase. This system can not only enhance the stimulation effect of tumor microenvironment but also allow an 8.7-fold enhanced PDT. Recently, Huo and Shi group<sup>162</sup> modified BP nanosheets with biocompatible photosynthetic cyanobacteria. Cyanobacteria may create O<sub>2</sub> by photosynthesis when exposed to a 660 nm laser, and BPNs can activate O<sub>2</sub> to produce <sup>1</sup>O<sub>2</sub> for PDT.

## Light Penetration

When light penetrates the tissue, it is absorbed or scattered, and the red light and NIR light have the greatest penetration depth ( $\lambda = 600\text{--}1350$  nm), usually 1–3 mm. In the past decades, the development of penetration depth of PDT was reviewed (Table 3).

Optimizing the chemical structure of SCPs can effectively improve penetration depth. First, heteroatom-doped SCPs can achieve two-photon excitation, such as N-doped GQDs, which shows the advantages of two-photon excitation PDT and generates more ROS.<sup>123</sup> Second, two-photon excited g-C<sub>3</sub>N<sub>4</sub> QD by reducing the size of g-C<sub>3</sub>N<sub>4</sub> was developed to achieve charge transfer transformation and improve penetration depth of light.<sup>84</sup> Third, adjusting the bandgap of SCPs can promote absorption edge redshift and enhance NIR absorption.

UCNP can convert NIR into UV and visible light.<sup>163</sup> For example, Hsiao combined hydrophilic g-C<sub>3</sub>N<sub>4</sub> with NaYF<sub>4</sub>: Yb<sup>3+</sup>/Tm<sup>3+</sup> upconversion nanoparticles through positive ligand polylysine. UCNPs can convert NIR into UV light and promote g-C<sub>3</sub>N<sub>4</sub> to release blue-green visible light.<sup>164,165</sup>

Microwaves can pass through all types of tissues and induce PDT for deep cancer. Zhang et al<sup>85</sup> reported an excellent microwave-induced g-C<sub>3</sub>N<sub>4</sub> QDs. In vitro cell experiment results show that g-C<sub>3</sub>N<sub>4</sub> QDs can enter osteosarcoma UMR-106 cells under microwave radiation and generate <sup>1</sup>O<sub>2</sub>, which enhances the microwave's lethal effect on tumor cells.

The Cherenkov radiation of X-ray and radionuclide can be used as internal light source, which is no longer limited by external light source penetration. The high energy of X-ray photons cannot directly excite PSs, but the high-energy ionizing radiation can be converted into UV or visible light through the energy medium (namely Cherenkov radiation), thus activating PSs.<sup>166</sup> For example, BP/Bi<sub>2</sub>O<sub>3</sub><sup>167</sup> and Bi<sub>2</sub>S<sub>3</sub><sup>168</sup> are highly efficient and biocompatible radiosensitizers that can be used in cancer cooperative radiotherapy. When the propagation speed of dielectric charged particles produced by the decay of radionuclides (eg,  $\beta^+$  and  $\beta^-$ ) is faster than that of light, Cherenkov radiation also occurs, which can emit UV and visible light (250–600 nm) in a wide energy range to activate PSs to generate ROS.<sup>88</sup> However, recently, there is no relevant report on radionuclide Cherenkov radiation-excited organic SCPs, which are commonly used in TiO<sub>2</sub> and porphyrin molecules, such as <sup>68</sup>Ga-TiO<sub>2</sub><sup>169</sup> and <sup>89</sup>Zr-porphyrin.<sup>170</sup>

The internal light source also includes chemiluminescence and bioluminescence. The chemiluminescence between luminol and hydrogen peroxide was used to activate semiconducting polymer to generate <sup>1</sup>O<sub>2</sub> with good anticancer and antifungal effects.<sup>171</sup> Furthermore, there is

**Table 3** Summary of Light Penetration Strategies

Materials	Light Penetration Mechanism	Reference
N-doped GQDs/adjusting g-C <sub>3</sub> N <sub>4</sub> size	Two-photon excitation	[84,123]
g-C <sub>3</sub> N <sub>5</sub> /Zn <sup>2+</sup> and K <sup>+</sup> -doped g-C <sub>3</sub> N <sub>4</sub>	Decrease bandgap	[86,87]
g-C <sub>3</sub> N <sub>4</sub> /UCNPs	Conversion of NIR into ultraviolet and visible light	[164,165]
g-C <sub>3</sub> N <sub>4</sub> QDs	Microwave induction	[85]
BP/Bi <sub>2</sub> O <sub>3</sub>	Cherenkov radiation of X-ray	[167]
MEH-PPV	Chemiluminescence	[171]
( <i>p</i> -Phenylene vinylene) derivative	Bioluminescence	[172]

**Abbreviations:** MEH-PPV, poly(2-methoxy-5-[(2-ethylhexyl)oxy]-*p*-phenylene vinylene); GQDs, graphene quantum dots; NIR, near-infrared; QDs, quantum dots.

a bioluminescent resonance energy transfer between luminol and organic photovoltaics. The oligomer (*p*-phenylene vinylene) derivative was activated by bioluminescence, which killed approximately 80% of cancer cells, and the inhibition rate of the tumor tissue was as high as 50%.<sup>172</sup>

## Targeting

The theoretical basis of nanomedicine is enhanced permeability and retention effect,<sup>173</sup> that is, macromolecules larger than 40 kDa selectively leak from tumor blood vessels and accumulate in tumor tissues, but not in normal tissues. However, recent studies have found that only 0.7% (median) of the nanoparticle injection dose reaches the tumor,<sup>174</sup> which requires biological strategies to solve nanodrug-delivery challenge. One way to overcome tumor-delivery barrier is to pair nanodrugs with the tumor to regulate the malignant tumor microenvironment and achieve effective accumulation of nanodrugs.

First, tumor cells targeting ligands mainly include antibodies or peptides,<sup>14,175</sup> hyaluronic acid (HA),<sup>158,176</sup> and folic acid (FA).<sup>25,177–179</sup> Ding et al<sup>14</sup> produced a compound of photosensitizer P50 modified with HER2 antibody, demonstrating the potential of HER2-SCPNs to target SKBR-3 tumors. Feng et al<sup>175</sup> covalently coupled surface carboxyl-modified P51 with antibody (anti-EpCAM), which can detect MCF-7 tumor cells and localize them on the cell membrane, to accomplish targeted imaging of distinct regions of tumor cells. Furthermore, Xu et al<sup>180</sup> modified semiconducting polymer with cyclic arginine glycine aspartate peptide, which can selectively kill  $\alpha\text{v}\beta 3$  integrin-overexpressing MDA-MB-231 cells. Second, SCPs can induce subcellular organelle-mediated cell death under light, such as lysosome and mitochondria. Triphenylphosphine bromide (TPP),<sup>72</sup> TAPP<sup>181</sup> and Met<sup>153</sup> have been used as mitochondrial targeting agents for SCPs. In addition to the two abovementioned types of organelles, there are the cell membrane and nucleus, and the detailed content can be referred to other reviews.<sup>1</sup> Lastly, in addition to biological strategies, magnetic targeting agent  $\text{Fe}_3\text{O}_4$ <sup>182,183</sup> can also be used to increase PS intracellular concentration to avoid systemic toxicity.

## Biosafety and Toxicity Evaluations of SCPs

The biological safety assessment of SCPs includes in vitro cellular uptake, localization, toxicity, in vivo biodistribution, degradation, excretion, material solubility, biodegradation, and biocompatibility. Metal-free SCPs essentially avoid the toxic and side effects of heavy metal ions and

small molecules on organisms. The main problem of linear SCPs and high crystallinity COFs is poor hydrophilicity, which has been mentioned in the previous section and will not be repeated here.

GQDs have smaller particle size, which cannot accumulate in the main organs and are quickly removed by the kidney, showing low cytotoxicity in vitro. Recently, some studies have evaluated the photodynamic cytotoxicity of GQDs in vitro and in vivo.<sup>22</sup> To further improve the solubility of GQDs, Li and Yi combined GQDs with PEG to improve its solubility and blood circulation.<sup>184</sup>

Block  $\text{g-C}_3\text{N}_4$  has high stability, which makes it difficult to dissolve and biodegrade. To meet the requirements of practical clinical application, it needs to be modified. The most common method is preparation of ultra-thin  $\text{g-C}_3\text{N}_4$  nanosheets or PEG modification.<sup>185</sup> Xie analyzed the viability of HeLa cells after incubation for 48 h by MTT and found that ultra-thin  $\text{g-C}_3\text{N}_4$  nanoplates had excellent biocompatibility. When the  $\text{g-C}_3\text{N}_4$  nanoplate concentration is as high as  $600 \mu\text{g mL}^{-1}$ , there was no significant loss of cell viability.<sup>186</sup>

The BP stability is poor when compared to other SCPs. In vivo, BP is biodegradable and creates nontoxic and biocompatible intermediates, such as phosphate and phosphite, that are suitable for biomedical applications.<sup>187</sup> The cytotoxicity of BP on L-929 fibroblasts was evaluated by Han et al<sup>188</sup> in terms of dosage and duration. The findings revealed that BP cytotoxicity was proportional to concentration and exposure duration and influenced by decreasing enzyme activity and membrane damage mediated by oxidative stress. There was no apparent cytotoxicity when the BP concentration was less than  $4 \text{ g mL}^{-1}$ . When BP comes into touch with oxygen, light, or water, interstitial oxygen will be incorporated, resulting in massive structural deformation.<sup>189</sup> As a result, it is necessary to modify its surface to prevent rapid degradation. For example, graphene, h-BN,<sup>187</sup> PEG,<sup>190</sup>  $\text{Al}_2\text{O}_3$ ,<sup>191</sup> titanium sulfonate ligand ( $\text{TiL}_4$ ),<sup>192</sup> aryl diazonium salt<sup>193</sup> and other surface coating methods can significantly increase stability and minimize degradation.

## Conclusions

This review describes the research progress of the application of metal-free organic conjugated polymer for PDT. SCPs as PSs have good optical properties, such as high photostability and easy surface functionalization. Progress has been achieved in the application of SCPs in phototherapy, and some issues have been discussed, such as hypoxia, low

permeability, targeting, biocompatibility, and safety. However, there are still some important issues to be solved.

1. The research of 2D and 3D SCPs for PDT, such as covalent triazine framework and HOF, is still in the early stage. Inspired by linear polymers, D-A structures of 2D and 3D SCPs can be designed. Optimization of material synthesis, high yield, surface functionalization, size, morphology, defects, heterojunction, and multifunctional composites could help improve ROS generation efficiency. Furthermore, modification of metal ions leads to pollution; thus, the concentration should be controlled in a clear range.
2. SCPs are large, and molecular weight is not single, so we need to further explore QDs and self-assembly of oligomers; balance surface functionalization, polymer size, and concentration; and prolong the action time of drugs in vivo. The operating parameters of in vitro and in vivo studies, such as irradiation intensity, irradiation time and drug dose, and injection mode, need to be normalized to facilitate control studies.
3. The combination of PDT with gene therapy, radiotherapy, photothermal therapy, chemotherapy, and sonodynamic therapy needs further exploration. PDT can also achieve accurate diagnosis and real-time evaluation of therapeutic efficiency through imaging. However, there is an obvious contradiction between the efficiency of multifunctional composites and PDT, for example, the absorption efficiency of light, binding mode (nonspecific binding, covalent binding and indirect covalent binding through biomolecular bridge), and load rate of drugs on SCPs. Therefore, we need to establish standards to balance various factors.
4. Most studies did not consider the potential effects of drugs on stem, red blood, and immune cells. Moreover, we need to consider the differences between mouse models and large mammalian and human tumors. Human tumors are rarely exposed like xenograft mouse models. Presently, the biosafety research on SCPs is still in the early stage. There are no toxicity studies on systemic biodistribution, tolerance threshold, degradation, and clearance rate to determine the long-term effects of potential toxicity on animals. Therefore, it is urgent to conduct more comprehensive physical and chemical properties (residual harmful solvents in the synthesis process),

nanoscience, and biosafety toxicity assessment of SCPs.

In conclusion, in view of the development of SCPs and new emerging technologies in the future for PDT improvement, it is believed that PDT will be recognized as an effective therapy in clinical cancer.

## Abbreviations

AIE, aggregation-induced emission; BP, black phosphorus; BPQD, BP quantum dots; COF, covalent organic framework; CTF, covalent triazine framework; EC, edge of the conduction; EV, edge of the valence; FA, folic acid; FRET, fluorescence resonance energy transfer; GQD, graphene quantum dots; HOF, hydron-bonded organic frameworks; HOMO, highest occupied molecular orbital; ISC, intersystem crossing; LUMO, lowest unoccupied molecular orbital; MOF, metal-organic framework; PS, photosensitizers; QD, quantum dots; ROS, reactive oxygen species; SCPs, semiconducting conjugated polymers.

## Consent for Publication

The authors confirm that the details of any images can be published.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest for this work.

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