Black phosphorus (BP) constitutes a new class of two-dimensional materials with multiple biomedical functionalities and applications. Possessed with outstanding advantages of large surface area, intrinsic photoacoustic properties, excellent biocompatibility, and selective toxicity to tumor cells, BP is becoming an ideal candidate in multifunctional cancer theranostics including photothermal therapy, photodynamic therapy, drug delivery, and bioactive phosphotherapy. This minireview summarizes recent progress pertaining to theranostic applications of BP nanosheets and black phosphorus quantum dots and discusses the prospects in advanced theranostics.

**KEYWORDS**
black phosphorus, bioactive phosphotherapy, drug delivery, photodynamic therapy, photothermal therapy

## INTRODUCTION

Black phosphorus nanosheets (BPs) with a two-dimensional (2D) structure have attracted enormous attention since they were isolated from the bulk materials.\(^1\) BPs consist of flexuous P atoms connected by P-P bonds forming a unique puckered honeycomb structure, and BP laminates have strong anisotropic...
compressibility and rigid zigzag interlayers. Because the layer number, direct bandgap, and carrier mobility can be tailored, BPs have excellent optical and electrical properties. Up to now, BPs have been used in antibacterial applications, photocatalysis, electrocatalysis, photodevices, optical devices, semiconductor devices, and three-dimensional printing scaffolds. BPs are unstable in aqueous and aerobic environments in which they degrade into phosphate ions rapidly. The production and store of BPs are usually in solvent like N-cyclohexyl-2-pyrrolidone (CHP) to prevent BPs from degradation. However, the degradation products are useful and have no harm to the human body thereby making BPs the ideal biodegradable materials while possessing good biocompatibility and multiple functionalities.

Multifunctional 2D materials have been explored for a variety of biomedical applications such as suppressing cancer mitigation, malignant migration, and multidrug resistance thus promoting advanced cancer theranostics. BPs are also interesting candidates in designing nanoplat-forms for cancer theranostic applications. For example, BPs have the advantages of efficient photothermal conversion and photonic singlet oxygen generation with a high quantum yield, by which BPs are regarded as promising photosensitizers in photothermal therapy (PTT) and photodynamic therapy (PDT) for cancer. Moreover, intrinsic to 2D materials, BPs possess a large surface-to-volume ratio rendering them efficient in loading functional molecules for drug delivery and bioimaging. Although the instability of BP can be a concern, some remedies have been proposed to improve the stability, for example, modification of metal ions, surface coating, and incorporation with other materials. Biodegradable polymers that are easily to be well-designed are commonly used to keep BP stable before functioning in physiological environment, such as the poly ethylene glycol, poly (lactic-co-glycolic acid) (PLGA), polydopamine, and the hydrogels. On the other hand, degradation of BP yields the ability of producing reactive oxygen species (ROS) in cells, which is shown to selectively cause cell cycle arrest in tumor cells but not normal cells, consequently making BPs potentially useful in chemotherapy.

Herein, recent advances of BPs in biomedicine such as cancer theranostic applications including PTT, PDT, radiotherapy (RT), drug delivery, bioactive phototherap-apy (BPT), and integrated bioimaging/theranostic are described (Figure 1). The prospects are discussed, and the applications of BPs are expected to spur broad inter-ests in the attempt to develop new cancer theranostic technologies.

**FIGURE 1** BPs in cancer theranostic applications such a PTT, PDT, RT, BPT, drug delivery, and integrated therapy. Image of PTT: Reproduced with permission. Copyright 2018, American Chemical Society; Image of PDT: Reproduced with permission. Copyright 2018, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim; Image of RT: Reproduced with permission. Copyright 2017, American Chemical Society; Image of drug delivery: Reproduced with permission. Copyright 2018, Proceedings of the National Academy of Sciences of the United States of America; Image of integrated therapy: Reproduced with permission. Copyright 2019, The Royal Society of Chemistry

## 2 | BP APPLICATIONS IN CANCER THERAPY

### 2.1 | Photothermal therapy

PTT is a noninvasive strategy that utilizes optical-absorbing agents to generate hyperthermia under light irradiation to kill tumor cells. Although many types of nanomaterials such as AuNPs, graphene, and polymer nanoparticles have been adopted for PTT under near-infrared (NIR) irradiation, the insufficient biocompatibility and clearance of the photosensitizers still cause concern. BPs delivering excellent NIR photothermal performance and being biodegradable inherently are ideal for PTT applications. Reports showed that the PLGA-coated black phosphorus quantum dots (BPQDs) have a high photothermal conversion efficiency and so the targeted tumors can be heated rapidly from 26.3°C to 58.8°C. Shao et al have reported a biodegradable photosensitizer incorporating a thermosensitive hydrogel with BPs. It exhibits the sol-gel transition under NIR irradiation giving rise to an additional
In order to improve the PTT efficiency of BPs, researchers have also applied mesenchymal stem cells loaded with BPQDs for targeted PTT as the carrier to deliver the particles to glioma tumor cells, which have a tumor-tropic migration and enhanced PTT effect.

### 2.2 Photodynamic therapy

Different from PTT, PDT uses photoexcitation to activate photosensitizers to produce highly cytotoxic singlet oxygen ($^1O_2$) species to kill cancer cells. BPs and BPQDs are metal-free 2D materials with broad light absorption, excellent photodynamic effects, and robust ROS generation efficiency under light irradiation so that cancer cells can be killed effectively. Hence, BPs are used as biocompatible and powerful photosensitizers in PDT. However, a drawback of PDT is that the oxygen-dependent therapy loses efficiency under hypoxic conditions in the tumor microenvironment. To overcome this hurdle, researchers have reported a BP-nanosheets-based self-supporting oxygen system that catalyzes excess intracellular H$_2$O$_2$ to O$_2$ by well-designed heme oxidation, which can offer enough oxygen for PDT, consequently resulting in a 8.7-fold increase in the PDT efficacy in treating hypoxic cells.

Liu and the co-workers have investigated metal-organic frameworks incorporated with BPQDs inside as photosensitizers and catalase as an O$_2$ supporter outside. This system shows a high quantum yield of singlet oxygen and enhanced therapeuticeffects against hypoxic tumor cells.

### 2.3 Radiotherapy

Cancer RT based on high-energy X-ray radiation to trigger tumor ablation via DNA damage or cytotoxic free radicals induces cell apoptosis. Unfortunately, traditional RT produces unavoidable and excessive radiation, which can cause serious side effects and impair tissues in the vicinity. The outstanding properties of BPs including the direct bandgap, broad light absorption, high photothermal conversion efficiency, and high singlet oxygen generation efficiency make BP excellent RT sensitizers. X-ray-induced photodynamic therapy that combines the advantages of RT and PDT has been developed. Chan et al have reported a BPQDs-based RT sensitizer for precise tumor radiosensitization. This sensitizer uses polypeptide motif ArgGly-Asp-Gys in tumor targeting and a dimethylmaleic anhydride shell for surface charge switching to improve tumor accumulation and cell uptake in addition to PLGA to avoid off-target release. The tumor treated with the sensitizer shows overproduction of ROS and X-ray-induced cell apoptosis. Huang et al have prepared BP/Bi$_2$O$_3$ heterostructures for efficient and synergistic cancer RT. The loaded Bi$_2$O$_3$ not only inhibits rapid degradation of BPs, but also imposes synergistic effects on $^1O_2$ production under X-ray irradiation to improve the radiotherapeutic activity in the treatment of melanoma.

### 2.4 Bioactive phosphotherapy

The concept of “bioactive phosphotherapy” was firstly proposed by Yu et al by taking advantage of the inherent chemotherapeutic anticancer effects of BPs. BPs are unstable in aqueous media and break down to form phosphate anions under physiological conditions. Participation of water, oxygen, and redox-active groups in BPs degradation leads to ROS generation and subsequent cytotoxicity. It has been shown that bare BPQDs induce higher cytokines release and significant inflammation response in mice serum, whereas titanium sulfonate ligand-modified BPs (TiL$_4$@BPs) with higher stability proved to lead to lower degree of inflammation. Zhou et al have found that BPs are more bioactive in tumors than normal cells confirming the selective chemotherapeutic effects. Intracellular biodegradation of BPs and production of phosphate anions are faster in three types of cancer cells than in normal cells. Stronger intracellular oxidative stress and significant G2/M phase arrest are observed from BP-treated tumor cells, but normal cells are not affected.

An explanation of the different cytotoxicity may be that higher energy metabolizing rates, more prominent cellular uptake of BP nanosheets, and faster intracellular degradation occur in cancer cells compared to normal cells. The degradation-associated bioactivity of BPs exhibits ideal selectivity in killing tumor cells, which is superior to that of the traditional chemotherapeutic agent, doxorubicin. The distinct degradation performance of BPs makes the materials suitable as not only PTT/PDT photosensitizers, but also bioactive phosphorus chemotherapeutic reagents.

### 2.5 Drug delivery

Drug delivery systems based on 2D materials have been widely used in maintaining the drug concentration and...
sustaining drug circulation. Biodegradable BPs with large surface-to-volume ratio and extraordinary photonic properties are regarded to be the ideal drug delivery platform in cancer therapy. Zhou et al. have used BPs to load three nuclear localization signals (NLSs) for gene editing with a drug loading capacity of 98%. The enriched NLSs are released after degradation of BP nanosheets in the cytoplasm and lysosome. By exploiting the photothermal transition ability, BPs have been utilized in light-controlled drug release to yield synergistic PTT effects. Wang et al. have prepared a light-triggered drug delivery system by loading SrCl$_2$ onto BPs with the outside PLGA shell in order to prevent off-target release. Sr$^{2+}$ release is controlled by a laser and BP-based local hyperthermia that destroys the PLGA shell produces enhanced therapeutic effects arising from the photothermal process. Qiu et al. have proposed the concept of “biodegradable drug delivery systems” using BP-incorporated agarose hydrogel nanosheets as a biodegradable delivery platform to achieve precise and light-controlled in situ drug delivery and conduct chemophotodynamic/PTT for efficient tumor killing. All in all, these and other drug delivery systems take advantage of the excellent properties of BPs such as the high loading capacity, superior photonic performance, and good biodegradability to control burst release precisely and keep the drug concentration within the therapeutic window.

### 2.6 Integrated therapy

A new field of nanomedicine based on BPs and functional imaging molecules has been proposed to integrate cancer...
diagnosis and therapy.\textsuperscript{52} Wang et al describe a strategy by using Nile blue (NB) dye to modify BP nanosheets in order to combine PTT and NIR imaging to accomplish comprehensive therapy.\textsuperscript{53} Metal nanoparticles with imaging capabilities such as Ln, MnO$_2$, and Fe$_3$O$_4$ are introduced to BPs to combine therapy with fluorescence imaging or magnetic resonance imaging to achieve enhanced PDT and to monitor the therapeutic effects and prognosis.\textsuperscript{54-56} BPs modified with fluorescence molecules have also been proposed for integrated therapy.\textsuperscript{57,58} Wang et al have prepared a system with chlorin e6 (Ce6)-loaded BPs for organelle-targeting therapy in combination with PTT/PDT with in vivo tumor fluorescence imaging. Mitochondria-targeted PTT/PDT and hyperthermia occur in the tumor cells and ROS production is also promoted in the mitochondria by Ce6. The tumor illuminance shows that the particles accumulate in the tumor after 12 h, which is the best time for PTT/PDT therapy. The system exhibits remarkable therapy efficiency and greatly inhibited tumor growth.\textsuperscript{52}

3 | CONCLUSION AND PERSPECTIVES

As a fledgling class of 2D materials with excellent and unique properties, BPs have promising prospects in biomedical applications especially cancer therapy. This minireview summarizes recent progress related to the application of BPs to different tumor therapies such as PTT, PDT, RT, BPT, and diagnosis-combined therapy. Owing to the good photothermal conversion and photoexcitation properties, BPs are widely used in PTT, PDT, and RT. More importantly, BPs with selectively in vivo degradation performance that the degradation rates and toxicity in tumor cells are higher than those in normal cells, facilitates BPs inherent anti-tumor properties. Furthermore, BPs have large surface-to-volume ratios as well as good biocompatibility and biodegradability rendering them ideal in degradable drug delivery systems. On account of these advantages, BPs have large potential as multifunctional materials in integrated cancer diagnosis and therapy. To meet the needs of less side-effects and higher clearance ratio of cancer cells, BPs have also displayed promising potential in the immunotherapy. A personalized PTT vaccine formulation of BPQDs loaded in nanovesicles derived from surgically removed tumor cell membrane was proved to have an efficient immune clearance of surgical residual tumor cells.\textsuperscript{59,60} However, the applications of BP toward the clinical medicine still have some challenges. Typically, like other biodegradable materials, BP is instable in the physiological environment. Thus, suitable drug formulations of BP should be established, which can maintain BP in stability at the period of cancer treatment and degrade after the treatment. In summary, BPs with many unique inherent properties are expected to play an important role in advanced theranostics in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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