Research article

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Facile sonochemical-assisted synthesis of orthorhombic phase black phosphorus/rGO hybrids for effective photothermal therapy

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Abstract: Two-dimensional black phosphorus (BP) has been demonstrated to be promising in photoelectronic devices, electrode materials, and biomedicine owing to its outstanding properties. However, the application of BP has been hindered by harsh preparation conditions, high costs, and easy degradation in ambient condition. Herein, we report a facile and cost-effective strategy for synthesis of orthorhombic phase BP and a kind of BP-reduced graphene oxide (BP/rGO) hybrids in which BP

remains stable for more than 4 weeks ascribed to the formation of phosphorus-carbon covalent bonds between BP and rGO as well as the protection effect of the unique wrinkle morphology of rGO nanosheets. Surface modification BP/rGO hybrids (PEGylated BP/rGO) exhibit excellent photothermal performance with photothermal conversion efficiency as high as 57.79% at 808 nm. The BP/rGO hybrids exhibit enhanced antitumor effects both *in vitro* and *in vivo*, showing promising perspectives in biomedicine.

Keywords: cancer; sonochemical; black phosphorus; orthorhombic phase; hybrid; photothermal therapy.

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1 Introduction

Two-dimensional (2D) materials have aroused enormous research interest around the world since 2004 due to their remarkable properties [1, 2]. Graphene [1], Au nanoparticles [3], hexagonal boron nitride (h-BN) [4], transition metal dichalcogenides (TMDs) [5, 6], and metal-organic frameworks [7–10] have been extensively studied in photoelectronic devices [11, 12], flexible electronic devices [13, 14], batteries [15], and promising biomedical applications [16–20]. Recent focus has shifted to the emerging perovskite [21], Mxene [22–25], and various 2D mono-element layered materials (e.g. black phosphorus [BP] [26–30] antimonene [31–34], bismuthine [35], and boron [36]). BP possess outstanding advantages in comparison with other 2D materials because of its intriguing physicochemical features, i.e. thickness tunable bandgap (0.3–2.0 eV) [26] which bridges the space between zero-gap graphene [37] and large-gap TMDs (1–2 eV) [20], high carrier mobility [38], and unique properties of biocompatibility and degradability with nontoxic degradation products (phosphate and phosphonate [39–41] that exist in the human body) [42, 43], thus holds great potential in bio-related areas, such as photothermal therapy (PTT) [44, 45], photodynamic therapy [46], photoacoustic imaging [47], and drug release [48] for cancer theranostics.

BP was firstly derived from white phosphorus at high temperature and high pressure [49]. However, the synthesis of BP has been subjected to harsh preparation conditions and high costs. BP can be obtained by high energy mechanical milling (HEMM) from red phosphorus (RP), but the ball milling process is time-consuming and the crystallinity of the obtained BP is not optimized enough [50, 51]. Recently, chemical vapor transport has been developed to synthesize high-quality BP crystals [52–54], whereas mineralization additives are necessary in which poisonous substances may be involved. Therefore, to find a facile, cost-effective, and environmentally friendly strategy to prepare BP crystals is still urgent. Based on phase transition analysis (combining phase diagram with Gibbs free energy theory), it was considered that the conversion of RP to BP is a spontaneous process and can be obtained under low temperature and low pressure [49, 55–57]. Most recently, a sonochemical method had been developed by Deji Akinwande et al.; they demonstrated a new way to efficiently produce large-scale BP crystals under facile and safe conditions. However, the synthesized BP crystals were mainly in rhombohedral phase [58], other than the orthorhombic phase that is more commonly used [59].

BP has been reported to undergo degradation under ambient condition as its exposed lone pair of electrons

tends to react with water and oxygen under light excitation [60, 61], which limits BP's potentials in semiconductor industry and energy storage, especially in the electrochemical or biomedical applications. Hence, forming chemical bonds by pre-occupying the lone pair electrons in the structure of BP by other elements may be a valid strategy to address the issue of the instability of BP. In this regard, strategies such as P-O-P bonds [60], Te-doped [62], surface coordination via titanium sulfonate ligand [63], etc. were proposed. Recently, coating BP with graphene has been proved to be a proper procedure to prevent degradation of BP [64–66]. The stability of BP/rGO hybrid may be significantly improved under ambient conditions due to the coverage of BP with rGO in the hybrid and owing to the formation of covalent bonds between BP and rGO [51]. To date, rare work was about exploring BP/rGO hybrids as a novel nanoplatform in biomedicine for cancer therapy.

Herein, orthorhombic phase BP was synthesized via a facile and cost-effective sonochemical method directly from cheap, stable RP, during which no poisonous chemical reagents were involved. We then fabricated a novel BP/rGO hybrid composed of rGO and BP nanoparticles by combining sonication and annealing (Figure 1). Next, we studied the ambient stability and photothermal activities of the as-prepared BP/rGO hybrids, and finally, we demonstrated the BP/rGO hybrids as novel photothermal agents (PTAs) for effective cancer therapy both *in vitro* and *in vivo*, highlighting their promising perspectives as next-generation biomedicine.

2 Results and discussion

2.1 Synthesis and characterization

We firstly synthesized BP crystals via a sonochemical approach with RP as the original reactant and isopropanol as the solvent [67]. In the process of sonochemistry, chemical reactions occurred in microscopic regions by localized extremely high temperature and high pressure, which originated from the quick surge and collapse of abundant bubbles during sonication. By using this *in situ* synthesis method, it is expected that RP could convert to BP with high mineralization.

Figure 2A shows the powdery, black substances that were obtained after sonication. To identify whether these black substances were BP, high-resolution transmission electron microscope (HRTEM), X-ray diffractometer (XRD), and Raman spectroscopy were used. Lattice fringe with spacing ~ 0.218 nm that well matches the (002) planes

Figure 1: Schematic diagram of synthesis of PEGylated BP/rGO via sonochemical approach and developed as BP/rGO-based photothermal therapy agent for cancer therapy.

of BP crystals was observed in HRTEM image (Figure 2B, marked by yellow dotted line). Interestingly, some amorphous substances can be observed in the vicinity of the lattice fringe (Figure 2B, marked by red arrow), which were attributed to RP since commercially available RP adopts the amorphous and adopted zig-zag ladder structure [68] (Figure 1) as confirmed by XRD pattern, where only three bulges were observed without sharp characteristic peaks (Figure S1). Raman spectra in Figure 2C clearly reveals the evolution process of the mineralization from RP to BP, which strongly confirms that RP has been first converted to RP-BP mixture (i.e. RP-BP hybrid) and then completely to BP crystals (eventually pristine BP crystals were obtained), whose Raman spectra are consistent with that of commercially available BP crystals. The optical microscopic image captured during Raman test also confirm the successful preparation of BP crystals (Figure S2, black region). To summarize, BP crystal was successfully synthesized via sonochemical method with amorphous RP as initial reactant.

Furthermore, the Raman out-of-plane vibration mode (A_g^{-1}) and the two in-plane vibration modes (B_{2g} and A_g^{+2}) of the BP crystals obtained herein locate at about 360, 440, and 466 cm^{-1} , respectively (Figure 2C), suggesting that they were mainly in orthorhombic phase, which

differs from that of BP mainly in rhombohedral phase (Raman vibration modes locate at about 392, 450, and 470 cm^{-1} , respectively) as in previously reported results [58]. The Raman spectra of the as-prepared BP crystals moves towards a lower wavenumber (blue shift) for 2.5 cm^{-1} , 5.2 cm^{-1} , and 5.5 cm^{-1} relative to the commercially available BP bulk crystals [44], respectively, which may imply the stacking-induced structural changes caused by the stacking effect in the process of transition from RP to BP or attributed to long-range Coulomb-layer interactions [69].

The successful synthesis of BP/rGO hybrids can be substantiated by HRTEM and scanning electron microscope (SEM). Firstly, a large number of dark, small particles adhering to the lamellar structure of graphene were found in TEM image (Figure 2D, denoted by yellow arrows). The particles showed a lattice fringe with spacing of ~ 0.34 nm in the HRTEM image, which well matches the (021) planes of the BP crystal (Figure 2D inset). Secondly, the SEM image shown in Figure S3A gives the fundamental morphologies of BP/rGO hybrids, in which intact, porous structures of graphene after annealing were found. Energy dispersive spectrometer (EDS) mappings confirm the uniform distribution of phosphorus element (Figure S3B–D). Besides, wrinkle morphology and lattice fringe (lattice distance of

~0.35 nm that is consistent with the (002) crystal plane of rGO) in HRTEM image were clearly observed, indicating the presence of graphene (Figure S4). Furthermore, the loading efficiency of BP onto rGO was calculated to be 21.42% (in mass ratio of phosphorus to total mass) by energy dispersive X-ray spectroscopy (Figure 2E). On the basis of the above morphological and structural characterizations, we conclude that BP/rGO hybrids with loading efficiency of BP at 21.42% were successfully fabricated.

To reduce the lateral size of BP/rGO hybrids to meet the demands of biomedical applications, the as-prepared

BP/rGO hybrids were ground with a grinding pestle for more than 30 min followed by sonication and centrifugation. As shown in Figure S5A and B, the average lateral sizes of BP/rGO decreased from larger than 1 μm (with thickness of ~3 nm, corresponding to few layers of rGO) to less than 200 nm (with thickness of ~2 nm), a relatively suitable lateral size enabling nanomaterials for passive targeting to tumor sites via enhanced permeability and retention effect [45].

In order to improve the dispersion in physiological solutions and enhance the tumor targeting effect, we

Figure 2: Synthesis and characterization.

(A) Photographs of BP bulks (black powder) prepared by sonochemical method. (B) HRTEM image of a typical intermediate product, i.e. RP-BP hybrid, in which the lattice of BP is clearly observed, and in the vicinity of BP exists amorphous RP, evidence of the conversion of RP to BP. (C) The evolution process of Raman spectra corresponding to the mineralization from RP to BP, revealing that RP firstly converted to RP-BP hybrid and finally to pristine BP. The Raman spectra of commercially available BP bulks are shown for comparison. The Raman spectra were collected under 532.1 nm laser excitation. TEM morphologies of BP/rGO (D; inset shows a typical HRTEM image of dark, small particles in D; scale bar, 2 nm) and PEG-coated BP/rGO (F; inset shows an enlarged image of a typical PEG-coated BP/rGO particle; scale bar, 100 nm), respectively. (E) Energy dispersive X-ray spectroscopy analysis of the BP/rGO. (G) FTIR spectra of the BP/rGO before and after PEG coating and compared with that of pristine DSPE-PEG-FA. (H) Zeta potential of the as-prepared BP/rGO before and after PEG coating in water.

chose 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[folate-(polyethyleneglycol)] (DSPE-PEG-FA) to modify the surface of BP/rGO hybrids [31]. The TEM image in Figure 2F indicates that spherical particles with average size of ~ 108.6 nm were found. The HRTEM image in Figure 2F inset shows that BP/rGO hybrids were successfully coated by DSPE-PEG-FA. The EDS mapping image (Figure S6) captured during HRTEM test reveals that the chemical composition of the PEG-coated BP/rGO is mainly carbon, oxygen, and phosphorus. Most of the carbon and oxygen covered in and around BP/rGO, while most of the phosphorus was distributed inside the spherical PEG-coated BP/rGO. Considering that DSPE-PEG-FA is mainly composed of carbon and oxygen elements, the successful modification of BP/rGO by DSPE-PEG-FA is confirmed. Fourier-transform infrared spectroscopy (FTIR) was further employed to identify the chemical compositions of BP/rGO before and after PEG coating. The absorption bands at ~ 2916 , 1113 , 1660 , and 1458 cm^{-1} correspond to the saturated C-H stretching vibration absorption, C-O-C stretching vibration (δ_{as}) absorption, C=O stretching vibration absorption, and C-C stretching vibration absorption in the DSPE-PEG-FA segments, respectively (Figure 2G).

Comparing these bands with that of BP/rGO and pristine DSPE-PEG-FA, the successful coating of BP/rGO with DSPE-PEG-FA is further confirmed. The Zeta potential of BP/rGO increased from -42.4 mV before coating to -20.6 mV (Figure 2H) after coating, proving the excellent dispersibility of BP/rGO after coating.

2.2 Stability of BP/rGO in ambient and in bio-fluids condition

To assess the ambient stability of BP/rGO, laser confocal Raman microspectroscopy and X-ray photoelectron spectroscopy (XPS) were utilized. After the as-prepared BP/rGO was exposed to ambient condition for 30 days, negligible changes (in peak intensity and position) were found in the Raman spectra (Figure 3A), suggesting the excellent ambient stability of BP/rGO. To further understand the improved stability of BP in BP/rGO, the freshly made BP/rGO were examined by XPS. A typical XPS full range spectrum of the freshly fabricated BP/rGO hybrid shown in Figure S7 indicates that the chemical composition is mainly carbon, oxygen, and phosphorus,

Figure 3: Stability of BP/rGO in ambient condition and in bio-solution.

(A) Raman spectra of BP/rGO before and after storage in ambient condition for 30 days. The Raman spectra were collected under 532.1 nm laser excitation. (B, C) XPS spectra with high resolution of freshly made BP/rGO, which correspond to C_{1s} and P_{2p} , respectively. (D, E) Absorption spectra of the PEG-coated BP/rGO, where PEG-coated BP/rGO hybrids were stored in PBS and in DMEM medium for 4 days (4°C), respectively. Insets in (D, E): photographs and variation of the absorbance normalized ratios (A/A_0) at 808 nm. (F) Changes of hydrodynamic sizes of PEG-coated BP/rGO over time, where PEG-coated BP/rGO hybrids were dispersed in PBS and in DMEM medium, respectively.

consistent with the results of EDS mapping (Figure 2E). In the core level of C_{1s} (280–293 eV), phosphorus-carbon (P-C) bonds related sub-bands with atomic percentage of ~1.89% (Figure 3B) can be divided. While in the core level of P_{2p} (125–140 eV), a P-C bonds related sub-bands can also be divided, with its atomic percentage up to 7.49% (Figure 3C). These P-C bonds related sub-bands in XPS analysis evidencing the formation of phosphorus-carbon covalent bonds [70]. It has been reported that robust P-C bonds can be induced in the process of HEMM, sonication, or annealing [51, 71, 72]. We thus reasonably speculated that these P-C covalent bonds contributed to lower the degree of oxidation of BP and to improve the stability of BP in ambient condition. Besides, except for the characteristic sp^2/sp^3 state of carbon element that appeared at ~284.8 eV, other sub-bands assigned to C-O (285.8 eV), C=O (287.3 eV), and -COOH (288.9 eV) were also observed in the core level of C_{1s} (Figure 3B), which might have originated from the insufficient reduction of GO during the annealing process. The P_{2p} spectrum exhibits two contributions, centered at 129.6 and 130.5 eV (Figure 3C), assignable to $2p^{3/2}$ and $2p^{1/2}$ (resulting from the spin-orbit splitting) of the BP/rGO, respectively. Large sub-bands located at ~133.9 eV attributed to oxidized phosphorus (i.e. PO_x) as reported in previous literature [73], probably stem from the oxygen defects or surface suboxides in BP, which were introduced in the process of synthesizing BP or BP/rGO [74]. In view of the above XPS analyses, we conclude that the formation of P-C covalent bonds is a reasonable strategy to effectively improve the stability of BP in ambient conditions. Furthermore, the unique wrinkle morphology of rGO can effectively isolate BP from oxygen and water, which is also beneficial to decrease the degradation of BP [66].

To investigate the stability of PEGylated BP/rGO in bio-fluids, UV-vis and dynamic light scattering (DLS) were utilized. We firstly dispersed the PEG-coated BP/rGO in phosphate buffered saline (PBS) and in culture medium (Dulbecco's Modified Eagle Medium [DMEM]) respectively and stored at 4°C. The absorbance spectra were recorded daily over a period of 4 days. For both cases of PEGylated BP/rGO dispersed in PBS and DMEM, the absorbance spectra of the PEGylated BP/rGO exhibit only slight decrease (Figure 3D and E); their colors kept unchanged and without visible precipitant (Figure 3D and E inset, left) within 4 days of storage time. The inset histograms in Figure 3D and E show the variations of the normalized absorbance at 808 nm. The intensity (A) dropped by less than 20% in PBS and less than 13% in DMEM medium over a period of 4 days, indicating the stability of PEGylated BP/rGO in PBS and in DMEM. Secondly, DLS measurements were conducted. The hydrodynamic average sizes of

PEG-coated BP/rGO exhibit an increasing trend with time but less than 200 nm within 4 days of storage time for both dispersed in PBS and in DMEM medium (Figure 3F), highlighting the reasonable long-term stability of PEGylated BP/rGO in bio-fluids. Apparently, it is concluded that the PEGylated BP/rGO possesses enhanced stability both in PBS and in DMEM for a reasonable period and thus hold great potential for biomedical applications.

2.3 Near-infrared extinction coefficients and photothermal properties

Since BP has a layer-dependent direct band gap (from 0.3 to 2.0 eV) and graphene has a zero band gap, BP/rGO hybrid is expected to have broadband UV-vis absorption spectra, which are further expected to possess wonderful photothermal conversion performance in the near-infrared (NIR) region. All of the UV-vis absorbance spectra of PEGylated BP/rGO, bare BP/rGO (Figure S8), BP nanosheets (BPNS), GO, and rGO (Figure S9), which were measured at 808 nm with different concentrations (0.025, 0.05, and 0.1 g l⁻¹) in water, exhibit broadband absorption properties. Figure 4A shows the linear relationships of normalized absorbance over the optical path length of the cuvette (A/L, where L = 10 mm) for the dependence on the concentration (which was determined by inductively coupled plasma atomic emission spectroscopy) at 808 nm. By using Lambert-Beer law, the extinction coefficients of PEGylated BP/rGO, BP/rGO, rGO, GO, and BPNS were calculated as summarized in Table S1. Specifically, the extinction coefficient of BP/rGO (13.67 Lg⁻¹ cm⁻¹) is comparable to BPNS (14.56 Lg⁻¹ cm⁻¹) and rGO (14.68 Lg⁻¹ cm⁻¹), while is ~3-fold as that of GO (4.64 Lg⁻¹ cm⁻¹) in our experiments. It is worth noting that the extinction coefficient of BP/rGO surges up to 21.96 Lg⁻¹ cm⁻¹ after PEG coating. However, this value is lower than that of Ti₃C₂ nanosheets (29.1 Lg⁻¹ cm⁻¹) [22] and nano-rGO (24.6 Lg⁻¹ cm⁻¹) [18] but exceeds Au nanorods (3.9 Lg⁻¹ cm⁻¹) [44], antimonene quantum dots (5.58 Lg⁻¹ cm⁻¹) [31], and BP nanoparticles (2.1 Lg⁻¹ cm⁻¹) [47], highlighting the PEG-coated BP/rGO hybrid as novel promising PTAs.

Furthermore, photothermal conversion activities were tested, and the photothermal conversion efficiencies (PTCEs) of PEGylated BP/rGO, BP/rGO, rGO, GO, and BPNS were determined by a reported method [75]. As shown in Figure 4B, upon 808 nm laser illumination for 5 min, PEGylated BP/rGO hybrids show significant temperature increments of 6, 10, 21.2, and 30°C for power densities of 0.3, 0.5, 1.0, and 1.5 W cm⁻², respectively, while only an increment of 0.9°C for DI water is

Figure 4: NIR extinction coefficients and photothermal properties.

(A) The relationships of normalized absorbance over the optical path length of the cuvette (A/L , where $L = 10$ mm) for the dependence on the concentration (0.025, 0.05, 0.1, 0.2 g l^{-1}) at 808 nm. (B) Temperature increments vs. NIR irradiation on/off time of PEGylated BP/rGO aqueous solution (0.1 g l^{-1}) under various power densities (0.3, 0.5, 1.0, 1.5 W cm^{-2}). Deionized (DI) water was introduced here for comparison (in grey). (C) Comparison of time constants and photothermal conversion efficiencies of PEGylated BP/rGO, BP/rGO, rGO, GO, and BPNS at 808 nm. (D) Real-time temperature of PEGylated BP/rGO dispersed in PBS (0.1 g l^{-1}) upon 1 W cm^{-2} incident illumination for five on/off cycles. (E) UV-vis absorbance spectra and photographs (inset) of PEGylated BP/rGO before and well after 1–5 NIR irradiation cycles. (F) Variation of the normalized absorbance of PEGylated BP/rGO at 808 nm. The data were extracted from (E).

observed for power densities of 1.5 W cm^{-2} . As a comparison (Figure S10), the temperature increment of BP/rGO (22.0°C) is comparable to rGO (22.9°C) but surpasses GO (13.1°C) and BPNS (15.2°C) in our experiments. It is worth noting that it soars to a temperature increment of 23.7°C for BP/rGO after PEG coating. Figure 4C summarized the time constants (which were determined by the dependence of time over $-\ln(\theta)$) and the PTCEs at 808 nm. The PTCEs of rGO, GO, and BPNS were calculated to be 43.17%, 37.29%, and 26.86% in our tests, respectively. The PTCE of BP/rGO was determined to be 42.62%, close to rGO but surpass GO and BPNS, and the PTCE surges up to 57.79% for PEGylated BP/rGO, suggesting the wonderful photothermal performance of the as-prepared BP/rGO (and PEGylated BP/rGO).

To assess the heating stability of the as-prepared PEGylated BP/rGO, a typical experiment including five cycles with each cycle involving heating for 5 min followed by a cooling interval of 10 min was conducted. An 808 nm laser (1 W cm^{-2}) was used, and PEG-coated BP/rGO was dispersed in PBS with original concentration of 0.1 g l^{-1} . The temperature and the absorbance were recorded, and the

photographs were captured during the experiment. Both the colors and the absorbance were almost unchanged after five laser on/off cycles (Figure 4D–F), highlighting the excellent NIR laser induced thermal stability of PEGylated BP/rGO in physiological solution.

2.4 In vitro cell experiments

Inspired by the high PTCE of PEGylated BP/rGO, the photothermal activity of the PEGylated BP/rGO in SMCC-7721 cells was further assessed. After incubation with different concentrations (0, 0.05, and 0.1 g l^{-1}) of PEGylated BP/rGO and irradiation with 808 nm laser at a laser intensity of 1.0 W cm^{-2} for 5 min, SMCC-7721 cancer cells were co-stained using acridine orange (green fluorescence, live cells) and propidium iodide (PI; red fluorescence, dead cells), fluorescence images were also taken at different times (0, 6, and 12 h). At the time point of 6 h after the treatment, the cells mainly irradiated by NIR-light were killed, then a clear demarcation line between dead cells (red) and live cells (green) was also observed (Figure 5A).

Twelve hours after the treatment, all the cells in the same well died due to the photo-thermal effect. Furthermore, PEGylated BP/rGO dose-dependent photothermal eliminating effect was observed for SMCC-7721 cells (Figure 5B). The SMCC-7721 cancer cells were incubated with various concentrations of PEGylated BP/rGO for 4 h, then the cells were irradiated with an NIR laser (808 nm, 1.0 W cm^{-2}) for 5 min. Obviously, almost no cells survived after incubating with 0.1 g l^{-1} of the PEGylated BP/rGO and irradiated by NIR laser for 5 min (Figure 5C). These results clearly demonstrate the PTT efficacy of BP/rGO in promoting cancer cell death.

However, an ideal PTAs should not only meet the satisfactory PTCE but also the biosafety requirements at the same time [45, 76]. Therefore, we also examined the cytotoxicity of the PEGylated BP/rGO upon several types of cells. The standard Cell Counting Kit-8 (CCK-8)

cell cytotoxicity assay was used to determine the relative viabilities of MCF-7, SMCC-7721, B16, and L-O2 cells after incubation with the PEGylated BP/rGO of different concentrations (0.01 , 0.05 , 0.1 , and 0.15 g l^{-1}) for 24 h. No obvious cytotoxicity was observed for the human normal liver cell and the other three cancer cells even at a high concentration of 0.15 g l^{-1} , which indicates good biocompatibility and suitability of PEGylated BP/rGO for more biomedical applications (Figure 5D).

2.5 *In vivo* antitumor efficacy

Based on the excellent therapeutic effect of PEGylated BP/rGO *in vitro*, we further conducted a preliminary *in vivo* anti-tumor and biological safety evaluation to verify the PTT effect and potential bio-application of PEGylated BP/

Figure 5: *In vitro* cellular experiments.

(A) Fluorescence images of SMCC-7721 cancer cells stained with acridine orange (green, live cells) and propidium iodide (red, dead cells) upon the after incubation with 0.1 g l^{-1} of PEGylated BP/rGO and exposed to NIR laser (808 nm , 1.0 W cm^{-2}) for 5 min; the photos were taken at different times (0, 6, and 12 h). (B) Dose-dependent PTT effect of PEGylated BP/rGO for SMCC-7721 cancer cells upon irradiation with NIR laser (808 nm , 1.0 W cm^{-2}) for 5 min. Concentrations of PEGylated BP/rGO were 0, 0.05, and 0.1 g l^{-1} . (C) Relative viabilities of SMCC-7721 cells after photothermal eliminating of B). (D) Relative viabilities of MCF-7, SMCC-7721, B16, and L-O2 cells after co-incubation with different concentrations (0.01 , 0.05 , 0.1 , and 0.15 g l^{-1}) of PEGylated BP/rGO for 24 h. Error bars represent the standard deviations (SDs) calculated by three parallel samples.

Figure 6: *In vivo* IR thermal imaging and photothermal anti-cancer activities of PEG-coated BP/rGO.

(A) Real-time IR thermal photos of SMCC-7721 tumor-bearing nude mice exposed to a NIR-laser (808 nm, 1.0 W cm⁻², 5 min) after intratumor injection of PEGylated BP/rGO (10 μg per mouse). (B) Real-time temperature changes of tumor sites during laser exposure corresponding to A). (C) Typical photographs and corresponding growth curves of tumors collected from the mice treated with saline solution, PEGylated GO with NIR laser irradiation, PEGylated RP/rGO with NIR laser irradiation, and PEGylated BP/rGO with NIR laser irradiation. All the relative tumor volumes were normalized to the initial sizes. Data were shown as mean ± SD, ***p < 0.001, n = 5, Dunnett's multiple comparison test. (D) Body weight of nude mice measured every 2 days under various treatment conditions as shown in C). (E) H&E stained images of typical tissues from mice treated with G1 (saline solution), G2 (PEGylated GO with laser irradiation), G3 (PEGylated RP/rGO with laser irradiation), and G4 (PEGylated BP/rGO) with laser irradiation.

rGO in the final set of this contribution. In order to evaluate the photothermal properties *in vivo*, the near-infrared image and temperature change (ΔT) of nude mice were

recorded by thermal imager within 5 min of irradiation after intratumoral injection of saline solution and three kinds of PEGylated nano-materials (GO, RP/rGO, and BP/

rGO), respectively. ΔT of the GO group was only $\sim 11^\circ\text{C}$, while that for the PEGylated BP/rGO treated mouse was higher than 21°C , with more remarkable temperature rises during a 5 min irradiation period (Figure 6A and B). Based on the *in vivo* photothermal response, we further evaluated the anti-tumor effect *in vivo* to verify the enhanced PTT effect. The nude mice bearing SMCC-7721 tumors were separated into different groups—Group 1: saline (control), Group 2: PEGylated GO with laser irradiation, Group 3: PEGylated RP/rGO with laser irradiation, and Group 4: PEGylated BP/rGO with laser irradiation. The length and the width of the tumors were measured every 2 days, and the volume of the tumors was calculated. At the end of the experiment (day 14), all nude mice were euthanized, and tumors were collected. The tumors in Groups 2 and 3 grew quickly within 2 weeks, suggesting that only PEGylated GO or only PEGylated RP/rGO had not enough effect on inhibiting the tumor growth as compared with the control group. In contrast, striking therapeutic effects could be found in Group 4, indicating that enhanced anticancer effects could be achieved by using the PTT strategies of PEGylated BP/rGO (Figure 6C). After the photothermal treatments, no obvious sign of acute toxic side effects such as abnormal body weight issues could be observed in all the experimental groups (Figure 6D). To further evaluate the *in vivo* toxicity of PEGylated BP/rGO, the organs of the mice from all the groups were stained using hematoxylin and eosin (H&E) for histological analysis. As shown in Figure 6E, no significant damage was observed to the normal tissues, indicating that PTT treatment based on PEGylated BP/rGO had no observable toxicity towards healthy tissue.

However, more systematic experiments are still required to evaluate the detailed long-term biocompatibility of PEGylated BP/rGO for biomedical applications. Additionally, the complexities of the interactions between the BP and rGO still need more detailed research in our future investigations. Furthermore, this BP-based nanomaterial may be also developed as NIR-responsive sustained drug release system for cancer treatment in the near future.

3 Conclusions

In conclusion, orthorhombic phase BP crystals were synthesized via a facile and cost-effective sonochemical method simply from RP, and a new kind of hybrid, composed of BP nanoparticles and rGO, had been developed by combined sonication and annealing. The BP/rGO

hybrids endow improved stability of BP crystals under ambient condition due to the fact that BP crystals were covered with rGO in the hybrids and owing to the formation of P-C bonds between BP and rGO. PEGylated BP/rGO hybrids exhibit enhanced stability in bio-fluids and wonderful PTCE of $\sim 57.79\%$ (with extinction coefficient of $21.96 \text{ Lg}^{-1} \text{ cm}^{-1}$) at 808 nm. Both *in vitro* and *in vivo* experiments demonstrate the excellent therapeutic effect of PEGylated BP/rGO hybrids. This work not only opens up new strategies in synthesis of BP crystals and their hybrids, but also proposes a BP-based PTA with immense promise in future biomedicine.

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Contributions: W. Y. Liang, D. Wang, and X. H. Ren conceived the project and, together with L. P. Liu, S. Y. Bao, and H. Zhang, supervised the project. W. Y. Liang, X. H. Ren, and X. Qi prepared the BP/rGO hybrid and performed the characterizations. W. Y. Liang, X. H. Ren, and M. Qiu contributed photothermal experiments and analysis. D. Wang, C. C. Ge, H. Y. Wang, Q. Liu, and Z. Y. Du carried out the *in vitro* and *in vivo* experiments and analyzed the results. W. Y. Liang, D. Wang, Y. J. Xu, and Z. J. Li co-wrote the paper with all authors contributing to the discussion and preparation of the manuscript.

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