Supporting information

Tumor Reoxygenation and Blood Perfusion Enhanced Photodynamic Therapy using Ultrathin Graphdiyne Oxide Nanosheets

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Materials. Zinc chloride ($ZnCl_2$), hexabromobenzene, $Pd(PPh_3)_4$, tetrabutylammoniumfluoride (TBAF), 2, 2, 6, 6-tetramethylpiperidine (TEMP) were purchased from Energy Chemical. Trimethylsilylacetylene, butyllithium (a solution in THF, 1.6 M), and tetramethylethylenediamine (TMEDA) were purchased from Aladdin Reagents. 3, 3', 5, 5'-Tetramethylbenzidine (TMB) was purchased from TCI Chemicals (Japan). Other materials including tetrahydrofuran (THF), ethyl acetate, toluene, HCl, H_2SO_4, HNO_3, NaCl, $MgSO_4$, Na_2SO_4, $AgNO_3$, $FeCl_3$, petroleum ether, dichloromethane, acetone, ethanol, pyridine, *N*,*N*'-dimethylformamide (DMF), and copper foils were purchased from Sinopharm Chemical Reagent Co., Ltd. Unless otherwise stated, reagents and solvents were commercially obtained and use without further purification. Copper foils were pretreated by sonicating in 1 M HCl and acetone and ethanol for 10 min, sequentially, dried under a flow of N_2, and used immediately for growing graphdiyne. Deionized water (18.2 MΩ/cm) from a Milli-Q ultrapure system was used in this study. N_2 (99.999%), Ar (99.999%) was purchased from Nanjing Special Gas Factory Co., Ltd.

Synthesis of [(Trimethylsilyl)ethynyl]zinc Chloride Solution.[1] To a Schlenk flask containing dry THF (12 mL) and trimethylsilylacetylene (20.0 mmol, 2.83 mL) at -78 °C was added butyllithium (20 mmol) and stirred for 40 min. Then, a solution of $ZnCl_2$ (20 mmol, 2.726 g) in 23 mL of dry THF was added dropwise to the reaction mixture at -78 °C, and then allowed to reach room temperature and stirred for 3 h. (Note: $ZnCl_2$ was previously dried at 80 °C under vacuum for 12 h).

Synthesis of Hexakis[(trimethylsilyl)ethynyl]Benzene.[2] To another Schlenk flask,

2.00 mmol (1.104 g) of hexabromobenzene, 0.400 mmol (0.500 g) of $Pd(PPh_3)_4$, 25 mL of dry toluene, and a solution of 20.0 mmol of [(trimethylsilyl)ethynyl]zinc chloride in THF prepared by the above described method were added under a N_2 atmosphere in this order. The mixture was stirred under a N_2 atmosphere at 80 °C for 72 h. After 20 mL of 1 M HCl was added, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The residue was purified by column chromatography (silica gel, petroleum ether: dichloromethane = 10: 1) to yield hexakis[(trimethylsilyl)ethynyl] benzen (HEB-TMS) as pale yellow powder. And the HEB-TMS monomer was characterized by ^1H NMR spectrum, ^{13}C NMR spectrum, and Raman spectrum to confirm the successful preparation of HEB-TMS.

Synthesis of Graphdiyne (GDY). HEB monomer could be obtained after deprotection of HEB-TMS by TBAF and used immediately. To a solution of 66.7 mg HEB-TMS in 15 mL THF was added 0.6 mL TBAF (1 M in THF, 0.6 mmol) and stirred at 0 °C for 15 min. The solution was then diluted with ethyl acetate, washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo and the deprotected material was dissolved with 50 mL of acetone and added slowly in 2 h into the mixed solution: treated copper foils were added to the mixed solution of acetone, pyridine and TMEDA with a volume radio of 100: 5: 1 in a three-necked flask. Then the mixture was kept under an N_2 atmosphere at 50 °C for 24 h. It is noted that the experimental setup should be kept protection from light. After reaction, GDY were grown on the surface of copper foils. Finally, the GDY were washed with heated acetone and DMF

in turn to remove the unreacted monomer and oligomer, then dried under N_2 atmosphere.

Preparation of Graphdiyne Oxides (GDYO). The GDYO samples were prepared by oxidation treatment of pristine GDY. In detail, 50 mg of GDY powder was carefully added into the mixture of concentrated H_2SO_4 and HNO_3 with a volume ratio of 1: 2 at 0 °C. After being agitated 6 h, the mixture was poured into 200 mL of distilled water and collected by centrifugation. The product was washed with distilled water for several times and dried in air at room temperature, yielding the samples denoted GDYO.

Exfoliation of GDYO into Ultrathin Nanosheets. The ultrathin GDYO nanosheets were obtained by liquid exfoliation of the as-prepared GDYO in aqueous solutions. In a typical synthesis, GDYO powder (10 mg) was dispersed in 40 mL water with 0.05 mL of HCl. Then the suspension was subjected to ultrasonication for ~24 h (150 W, 40 kHz) at ~10 °C. The initially obtained suspension was then centrifuged at about 3000 rpm for 5 min to remove the residual unexfoliated and large aggregated nanosheets.

General Characterization. Transmission electron microscopy (TEM) images were observed on a Hitachi Model H-7650 transmission electron microscope with an accelerating voltage of 100 kV. Scanning electron microscopy (SEM) images were obtained using a FEI Sirion-200 field emission scanning electron microscope operated at 5 kV. Atomic force microscopy (AFM) images were obtained using a tapping mode from an Asylum Research MFP-3D AFM. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AC-400FT spectrometer (300 MHz). Raman spectra were collected using an LABRAM-HR Raman spectroscope equipped with a synapse CCD detector and a confocal Olympus microscope. A 514.5 nm He-Ne laser was used for

excitation. X-ray photoelectron spectroscopy (XPS) analyses were performed on a Thermo ESCALAB 250 X-ray photoelectron spectrometer with Al Kα X-rays as the exciting source. Optical diffuse reflectance spectra were collected at room temperature with a UV-*vis* spectrophotometer (DUV-3700, Shimazu). A white standard of $BaSO_4$ was used as a reference. UV-*vis* absorption spectra of the samples were recorded on a UV-*Vis* spectrophotometer (Shimadzu 3600). FTIR spectra were recorded on a Thermo-Nicolet 6700 spectrometer.

Photocatalytic Test. 10 mg of photocatalyst and 50 mL of H_2O with 0.01 M $AgNO_3$ or $FeCl_3$ as the sacrificial electron acceptor were put in a hermetic device mainly composed of a quartz tube and sealing components. Prior to the photocatalytic test, the device was purged with Ar flow to remove air. A 300 W Xe lamp (Perfect Light PLS-SXE 300) with visible-light irradiation (λ>420nm) and a laser (Xi'an Minghui Optoelectronic Technology, China) with 660 nm laser were used as the light source, respectively. The amount of O_2 evolved was measured by gas chromatography (SHIMADZU GC-2014, TCD). The photocatalytic tests were repeated for three times for each sample with relative error <10%. And the average oxygen evolution rate of GDYO can reach ~150.7 μmol/g/h and ~130.1 μmol/g/h using $AgNO_3$ and $FeCl_3$ as the sacrificial electron acceptor, respectively. Cycling photocatalytic tests were performed using the same way after the samples were collected and washed with water.

Singlet Oxygen ($^1O_2$) Test (TMB measurements). 0.4 mL of TMB aqueous solution was mixed with 40 mL of HAc/NaAc buffer solution (pH=3.5), then 1.0 mL of aqueous suspension of samples (2 mg/L) was poured into the mixture solution. A 300 W Xe

lamp with visible-light irradiation (λ>420nm) was used as the light source. The oxidation of TMB was evaluated by monitoring the absorbance of the mixture solution with a UV-*vis* spectrophotometer. The measurements were performed under air atmospheres.

Spin Trapping-ESR Test. For the detection of $^1O_2$, 500 μL of aqueous suspension of samples (2 mg/L) was mixed with 10 μL of 2, 2, 6, 6-tetramethylpiperidine (TEMP). After being illuminated for 60 s, the mixture was characterized using a Bruker EMX plus model spectrometer operating at the X-band frequency (9.4 GHz) at room temperature. A Xe lamp (λ>420nm) was used as the light source.

Measurements of Photothermal Effect. Aqueous solutions containing different amounts of samples were placed in a quartz cuvette and irradiated with a 660 nm laser (0.5 W/cm^2) for 5 min. The temperature was monitored and periodically measured by a digital thermometer with a thermocouple probe at 10 s interval.

Photothermal Conversion Efficiency (η=60.8%**)**. For measuring the photothermal conversion efficiency of GDYO, 1.0 mL of aqueous dispersion of GDYO (50 μg /mL) was irradiated with a 660 nm laser at a power density of 0.5 W/cm^2 for 10 min. Then the laser was shut down for cooling to ambient temperature. The plot of time versus negative natural logarithm of the temperature driving force was drawn for further calculation of η.

Photoelectrochemical Measurements. The measurements were conducted on a Metrohm Autolab PGSTAT302N potentiostat/galvanostat in a three-electrode cell system under irradiation of a 300 W Xe lamp under ambient conditions. Visible light

(λ>420nm) with a power density of 100 mW/cm^2 was used as the illumination source. The FTO glass (1×2 cm^2) coated materials as the photoelectrode, a Pt foil as the counter electrode, and Ag/AgCl electrode as the reference electrode. 1 cm^2 area of the working electrode was exposed to the solution. The cyclic voltammograms (CVs) in the OER region were obtained in 0.1 M phosphate buffer solution under visible light irradiation (scan rate: 50 mV/s).

Synchrotron Radiation Photoemission Spectroscopy (SRPES) measurements. The measurements were conducted to determine the valence band maximum (VBM) positions of both GDY and GDYO. SRPES experiments were performed at the Photoemission Endstation (BL10B) in the National Synchrotron Radiation Laboratory in Hefei, China. To obtain the secondary electron cutoff, an excitation of 168.4 eV was utilized. The binding energy (BE) was calibrated and referenced to the E_f of a gold foil. The work function (Φ) of samples was determined according to the equation Φ=hv-ΔE, where ΔE was the spectrum width, *i.e.* the energy difference between the secondary electron cutoff and the Fermi level of tested sample. In order to obtain the secondary electron cutoff, a -10 V bias was applied to the sample, which accelerated all the photoelectrons with higher kinetic energy (KE) to overcome the work function of the analyzer.

Modification of iRGD-peptides on RBCs (i-RBCs). RBC membranes were first extracted following previously published protocols with modifications.[3] Whole blood was first withdrawn from female Balb/c mice (6-8 w) obtained from Vital River Laboratories (Beijing, China) by removing eyeball using a tube containing a 100 μL of

heparin solution (100 U/mL). The whole blood was then centrifuged (5000 rpm, 5 min, 4 °C), following which the serum and the buffy coat were carefully removed. The resulting RBCs were washed with cold 1 × PBS for three times and were collected by centrifugation. Peptide solutions (FITC-peptide, peptide sequence: stearoyl-GSSKSPSKKKKKKPGDK-FITC or iRGD-peptide, peptide sequence: stearoyl-GSSKSPSKKKKKKPGDCRGDKGPDC, disulphide bridge; C1-C9, Purity >95%) (total 1 mL, final concentration of 10 μM) were mixed with RBCs solution (about 1 × 10^9 cells) and then incubated for 30 min at 37 °C. The cells were then washed with 1 × PBS for three times to remove free peptides. The fluorescence of iRGD peptides on the cell surface were visualized by CLSM (LSM 880, Carl Zeiss Inc., Germany).

i-RBM Extract. iRGD-peptide modified RBCs membranes (i-RBM) were extracted following previously published protocols with modifications.[3] The resulting RBCs were washed in ice cold 1× PBS prior to hypotonic medium treatment for hemolysis. The washed RBCs were suspended in 0.25 × PBS in an ice bath for 20 min and were centrifuged at 9000 rpm for 5 min at 4 °C. The hemoglobin was removed, whereas the pink pellet was collected. The i-RBM solution was sonicated by a microtip using VibraCell VCX 130 (Sonic and Material, Inc., Newtown, CT) set at 50% power (20 kHz, 130 W) for 5 min. The resulting vesicles were subsequently extruded serially through 1 μm, 400 nm, and then 200 nm polycarbonate membranes (Whatman, Maidstone, UK) using an Avanti mini extruder device (Avanti Polar Lipids, Inc., Alabaster, AL) for 11 times, respectively. The size of the RBM-derived vesicles was measured by DLS.

Preparation of PEG Modified GDYO Nanosheets (GDYO@PEG). Prior to PEGylation remold, the GDYO (10 mg) was dispersed in 10 mL of pure water and then mixed with 10 mg of poly(ethylene glycol)-pyrene (PEG, M_W =10 000Da) under sonication on ice for 1 h. After sonication, excess PEG molecules were removed by centrifugation at 12000 rpm and washed by water for three times. The resulted GDYO@PEG was re-suspended in pure water to form GDYO@PEG aqueous solution.

Coating of i-RBM with GDYO@PEG (GDYO@ i-RBM). 1 mL of GDYO@PEG (0.5 mg/mL) was mixed with i-RBM (0.5 mg RBM protein) *via* sonication for 5 min. GDYO@RBM were prepared similarly by replacing i-RBM with RBM.

SDS-PAGE Protein Analysis. To characterize the RBM proteins on surfaces, RBM, i-RBM, GDYO@RBM and GDYO@i-RBM were treated with SDS lysis buffer containing 1 mM PMSF. The protein concentration of lysates was determined using a BCA protein assay kit. GDYO@RBM and GDYO@i-RBM were purified by centrifugation at 5000 g at 4 ℃ for 30 min to remove the free RBM. A 30 μg protein aliquot of each extract was separated by electrophoresis in a 12% sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE). For protein characterization, the polyacrylamide gel was stained by coomassie brilliant blue according to the provided protocol before imaging.

Detection of O_2 Generation. GDYO-based aqueous solutions (50 μg/mL equivalent concentration of GDYO) pretreated with N_2 bubble to remove residual O_2, and the O_2 concentration were measured with a Foxy Fospor-R oxygen sensor (Ocean Optics, Dunedin, FL) before and 660 nm laser irradiation (New Industries Optoelectronics,

Changchun, China) (0.5 W/cm^2).

Detection of $^1O_2$. Solutions containing GDYO@PEG, GDYO@RBM, or GDYO@i-RBM (at 50 μg/mL equivalent concentration of GDYO) were mixed with *p*-nitrosodimethylaniline (100 μg/mL), imidazole (100 μg/mL), and then irradiated by 660 nm laser at the light power density of 0.5 W/cm^2 for different periods of time. The generation of $^1O_2$ would result in the bleaching of RNO absorption at 440 nm. The reduction of optical density at 440 nm thus reflects the production of $^1O_2$.

Photothermal Conversion. Nanosheets aqueous solution with equivalent GDYO concentrations (50 μg/mL) was irradiated by the 660 nm laser and monitored the temperature by infrared thermal imaging camera (Ti27, Fluke, Everett, WA). The 1×PBS was used as control under the same condition.

Cell Culture. Murine breast cancer EMT-6 cells were obtained from American Type Culture Collection (ATCC) and cultured at 37 °C in a humidified atmosphere containing 5% CO_2. The cells were cultured in normal DMEM culture medium (Gibco®, Thermo Fisher Scientific, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS, HyClone, Logan, UT) and 1% penicillin/streptomycin (Gibco®, Life Technologies, Grand Island, NY).

Immunofluorescence Staining for Cellular Hypoxia Evaluation. EMT-6 cells were seeded on coverslips in a 24-well plate at a density of 4 × 10^4 cells per well. After culturing overnight in modular incubator chamber (Billups-Rothenberg, Del Mar, CA) with 1% O_2, 5% CO_2 and 94% N_2 (hypoxia chamber), the cells were treated with different formulations. After incubation for 4 h, the cells were irradiated with 660 nm

laser (0.5 W/cm^2, 10 min). The cells were further co-incubation with pimonidazole hydrochloride (Hypoxyprobe-1^{TM} plus kit, Hypoxyprobe Inc., Burlington, MA) for 1 h, followed washed three times with PBS, and then the hypoxia and cell nuclei were stained by FITC-Mab1 (Hypoxyprobe-1^{TM} plus kit, Hypoxyprobe Inc., Burlington, MA, green) and DAPI (blue), respectively, according to the manufacturer's instructions. Coverslips were mounted on glass microscope slides with a drop of anti-fade mounting media, and then visualized by CLSM.

Detection of $^1O_2$ *In Vitro*. EMT-6 cells 4 × 10^4 were seeded in a 24-well plate and incubated overnight in hypoxia chamber, and then treated with different formulations for 4 h, following 660 nm laser irradiation (0.5 W/cm^2, 10 min) or not. The cells were incubated with a fluorescent marker, singlet oxygen sensor green reagent, SOSG (BestBio biotechnologies, Shanghai, China), in DMEM medium (10 μM) for 30 min in dark (37 °C). The cells were then washed with PBS and re-suspended in culture medium. All of the cells were immediately trypsinized and the fluorescence signals were detected using flow cytometry (Ex/Em = 488 nm/525 nm). For each sample, the mean fluorescence intensity of 1 × 10^4 cells was recorded to determine the intracellular content of $^1O_2$.

$^1O_2$ generation detected by CLSM: EMT-6 cells were seeded on coverslips in a 24-well plate at a density of 4 × 10^4 cells per well. After culturing overnight in modular incubator chamber, the cells were treated with above formulations. After incubation for 4 h, the cells were washed three times with PBS, and then $^1O_2$ positive and cell nuclei

were stained by SOSG (green) and DAPI (blue), respectively, according to the manufacturer's instructions and then visualized by CLSM.

Live and Dead Stain of Tumor Cells *in Vitro*. To evaluate the photodynamic and photothermal effect on EMT-6 cells, 1×10^5 EMT-6 cells were seeded in 12-well plates and incubated overnight. Cells were then incubated with fresh medium containing GDYO-based various formulations at different concentrations for 4 h, following L-histidine per-incubation or not at normoxia or hypoxia chamber. After being irradiated with the 660 nm laser (0.5 W/cm^2, 10 min), the cells were incubated for another 24 h. EMT-6 cells were co-stained by calcein acetoxymethyl ester (calcein AM) and propidium iodide (PI) kit (BestBio, Shanghai, China) to differentiate live (green) and dead (red) cells, respectively.

Animals and Tumor Model. Female Balb/c mice at 6~8 weeks of age were obtained from Vital River Laboratories (Beijing, China). All animals received care in compliance with the guidelines outlined in the Guide for the Care and Use of Laboratory Animals, and all procedures were approved by the University of Science and Technology of China Animal Care and Use Committee. The xenograft tumor model was generated by injection of 2×10^5 EMT-6 cells (100 μL) with 20% Matrigel (BD Bioscience, Franklin Lakes, NJ) into the right flank of Balb/c mice.

***In Vivo* Distribution and *Ex Vivo* Tumor Accumulation.** Female Balb/c mice bearing EMT-6 xenografts were intravenously injected with DiR-labeled GDYO@PEG, GDYO@RBM, and GDYO@i-RBM. The dose of DiR was 0.5 mg per kg mouse body

weight. At the preset times, *in vivo* fluorescence images were acquired on the Xenogen IVIS Lumina system (Caliper Life Sciences, Alameda, CA). Moreover, after 96 h post-injection, the organs of mice including heart, lung, liver, spleen, kidney, and tumor were collected. Then fluorescence images were also acquired on the Xenogen IVIS Lumina system as well.

Intravital Microscopy. Mice were sedated with isoflurane inhalation anesthesia 1.5~2% (v/v) isoflurane in O_2 and placed within a custom-designed imaging box. Mice were maintained under anesthesia on a heating pad kept at 37 °C. We used an inverted laser scanning microscope using a 10× air 0.45 NA objective lens for *in vivo* CLSM. To visualize vessels, FITC-labeled dextran (M_W=75000, 10 mg/mL, 100 μL) was injected *i.v.* 30 min before imaging for tumor vessel labeling, respectively. After 10 h injection, tumors were excised. Frozen tissue sections were stained with DAPI.

Tumor Temperature Monitoring During Laser Irradiation. EMT-6 tumor-bearing Balb/c mice were intravenous injection with GDYO@PEG, GDYO@RBM, and GDYO@i-RBM at an equivalent dose of 20.0 mg GDYO per kg mouse weight. After 24 h, the tumors irradiated with 660 nm laser at power density of 0.5 W/cm^2 for 10 min. Finally, the real time temperatures and infrared images were recorded using an infrared camera.

Immunofluorescence Staining for Hypoxia and ROS Evaluation. Mice bearing EMT-6 tumors were randomly divided into five groups including: (I) PBS + Laser, (II) GDYO@i-RBM - Laser, (III) GDYO@RBM + Laser, (IV) GDYO@RBM + Laser, and (V) GDYO@i-RBM + Laser at an equivalent dose of 20.0 mg GDYO per kg mouse

weight (n=3 for each group). After 24 h intravenous injection of the above formulations,

For immunofluorescence staining for tumoral hypoxia: the mice were *i.v.* injection of pimonidazole hydrochloride (60 mg/kg), following 660 nm irradiation (0.5 W/cm^2, 10 min) or not. The tumors were surgically excised at 90 min. Frozen tissue sections were interrogated with mouse monoclonal antibody FITC-Mab1, according to recommended procedure by the manufacturers. Cell nuclei and blood vessels were stained with DAPI and anti-CD31 antibody (Alexa Fluor 647, BioLegend, San Diego, CA), respectively.

For immunofluorescence staining for tumoral ROS: the mice were *i.p.* injection of DCFH-DA (3 mg/kg), following 660 nm irradiation (0.5 W/cm^2, 10 min) or not. The tumors were surgically excised and frozen tumor slices were prepared.

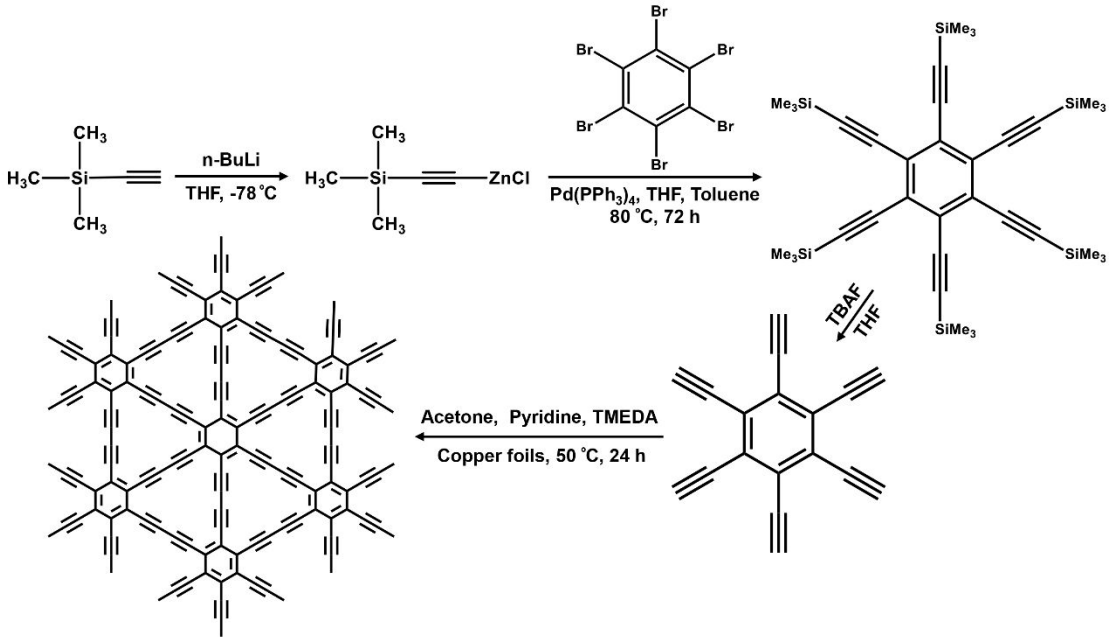
Images of the tumor immunofluorescence slide were acquired with the automated quantitative microscopy-based image analysis system TissueFAXS PLUS (TissueGnostics GmbH, Vienna, Austria) using the 20 × objective. TissueFAXS Viewer software (TissueGnostics) was used to determine the staining intensity of FITC and DAPI.

Antitumor Study. When the tumor volumes were around 100 mm^3, the EMT-6 tumor-bearing mice were injected *via* tail vein with various formulations (n = 6 for each group). At 24 h after injection, the mice were received irradiated with 660 nm laser at power density of 0.5 W/cm^2 for 10 min. Six formulations were used as below: (I) PBS Group, (II) GDYO@i-RBM, (III) Laser irradiation only, (IV) GDYO@PEG + Laser, (V) GDYO@RBM + Laser, and (VI) GDYO@i-RBM + Laser at an equivalent dose of 20.0

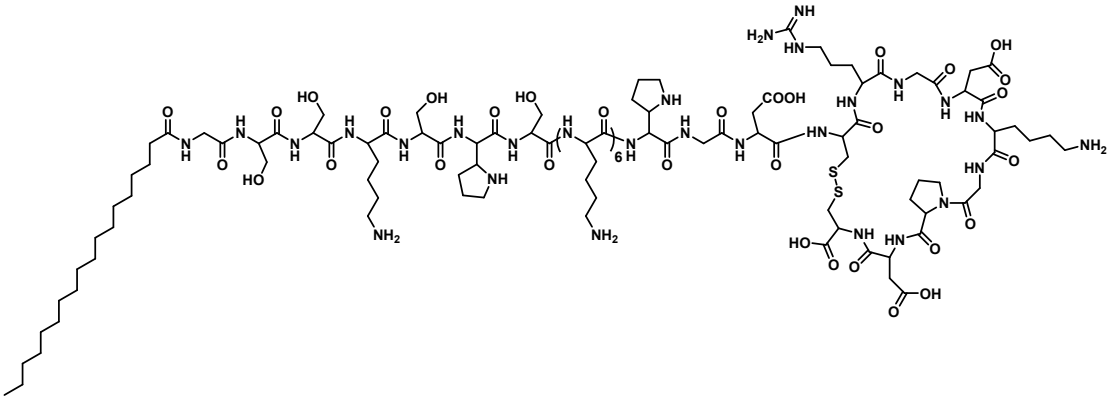
mg GDYO per kg mouse weight. The tumor growth was monitored by measuring the perpendicular diameter of the tumors (*i.e.*, length and width, respectively) using calipers every two days. The estimated volume was calculated according to the formula: Tumor volume (mm^3) = 0.5 × length × $width^2$. Weight of each mouse was also measured every two days.

Immunohistochemical and Immunofluorescence Analysis. The tumor tissues were fixed in 4% formaldehyde and embedded in paraffin. Subsequently, the tumor tissues were observed *via* H&E staining. Cell proliferation in tumor tissues were analyzed by immunohistochemical staining of proliferating cell nuclear antigen Ki67 monoclonal antibody (Santa Cruz Biotechnology, Dallas, TX).

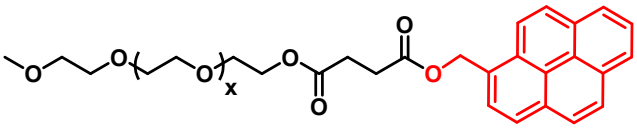
Statistical Analysis. The statistical significance was assessed using Student's t-test (two-tailed); $*P < 0.05$ was considered statistically significant in all analysis (95% confidence level).



Scheme S1. The synthetic route of graphdiyne (GDY).



Scheme S2. Chemical structure of iRGD peptide anchor.



Scheme S3. The structure of PEG-pyrene, which was synthesized according the report with minor modifications.[4]

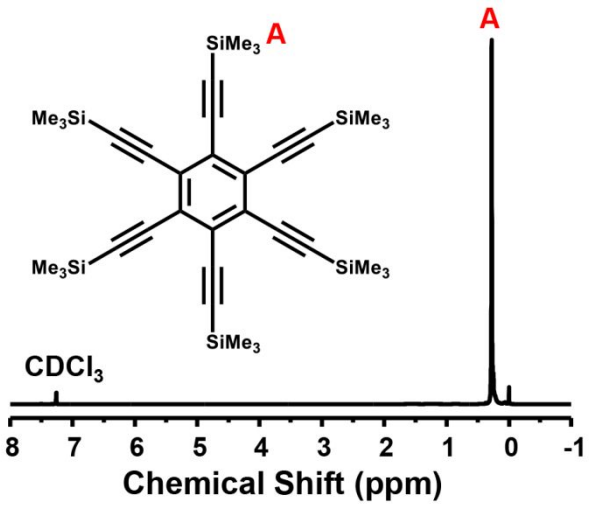


Figure S1. ^{1}H NMR spectrum of HEB-TMS ($CDCl_3$, 300 MHz).

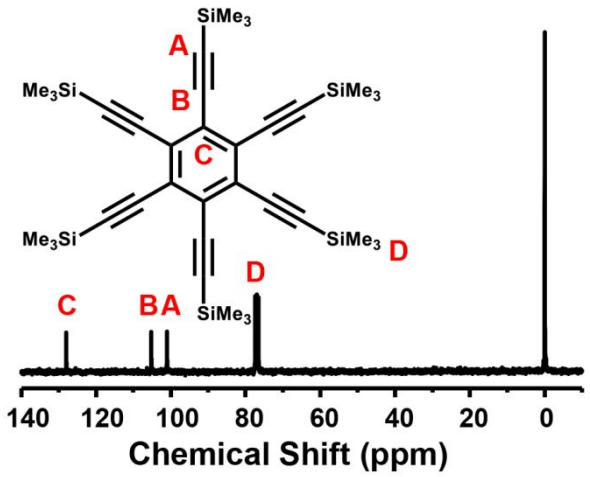


Figure S2. ^{13}C NMR spectrum of HEB-TMS ($CDCl_3$, 75 MHz).

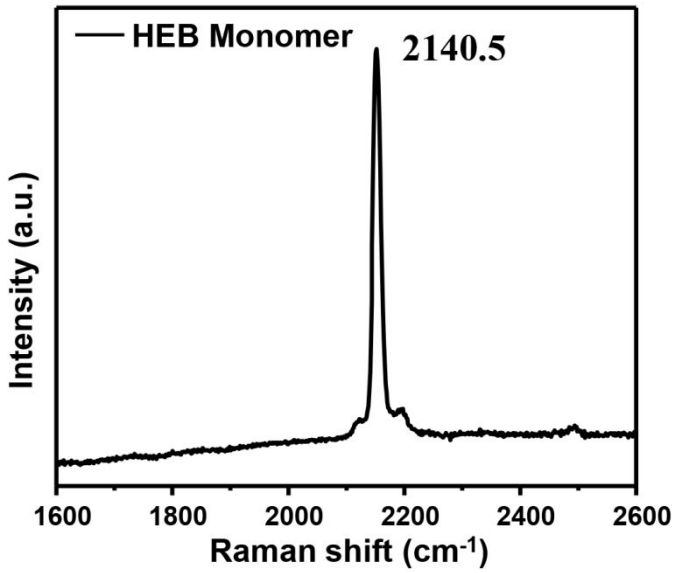


Figure S3. Raman spectrum of HEB-TMS.

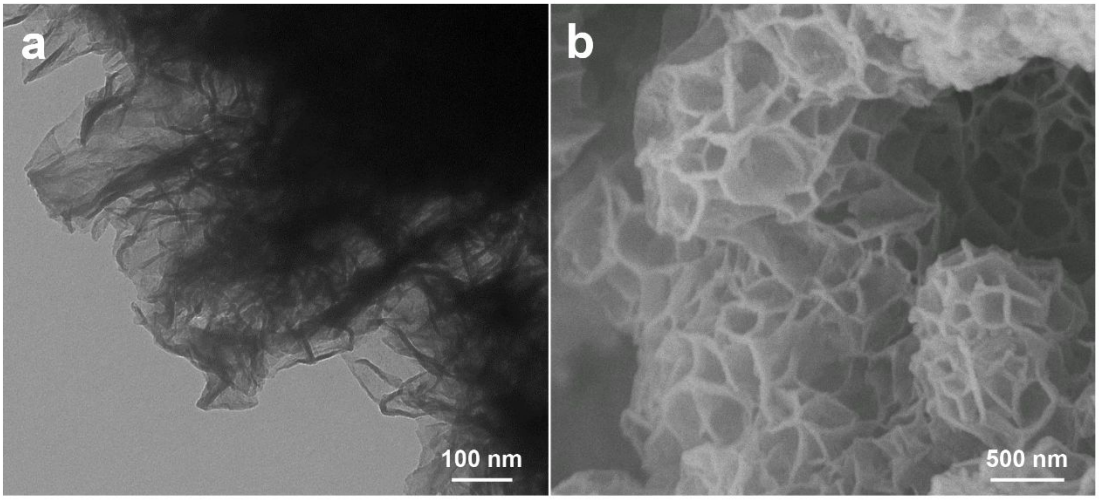


Figure S4. (a) TEM image and (b) the corresponding SEM image of the as-synthesized GDY.

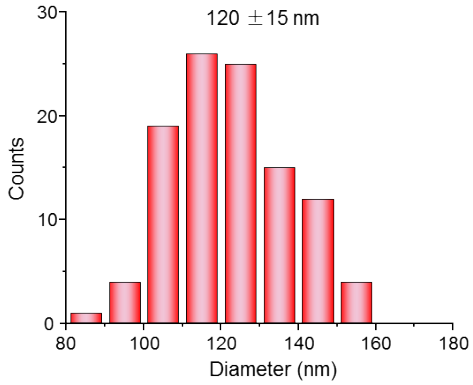


Figure S5. The size distribution of GDYO nanosheets.

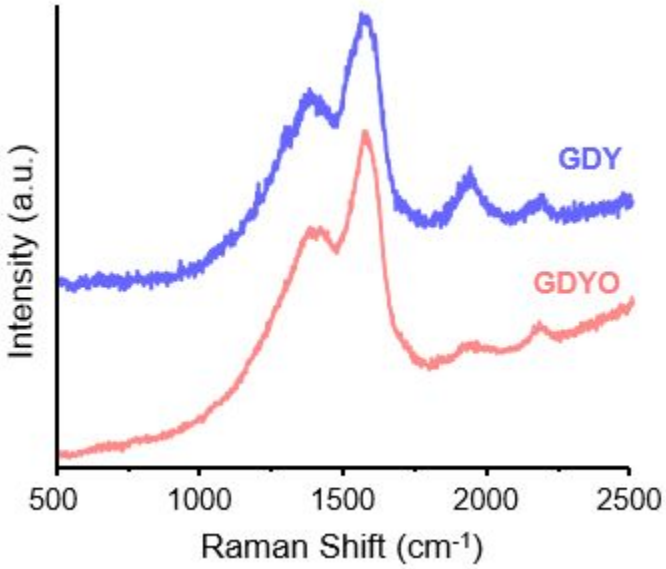


Figure S6. Raman spectra of GDY and GDYO nanosheets.

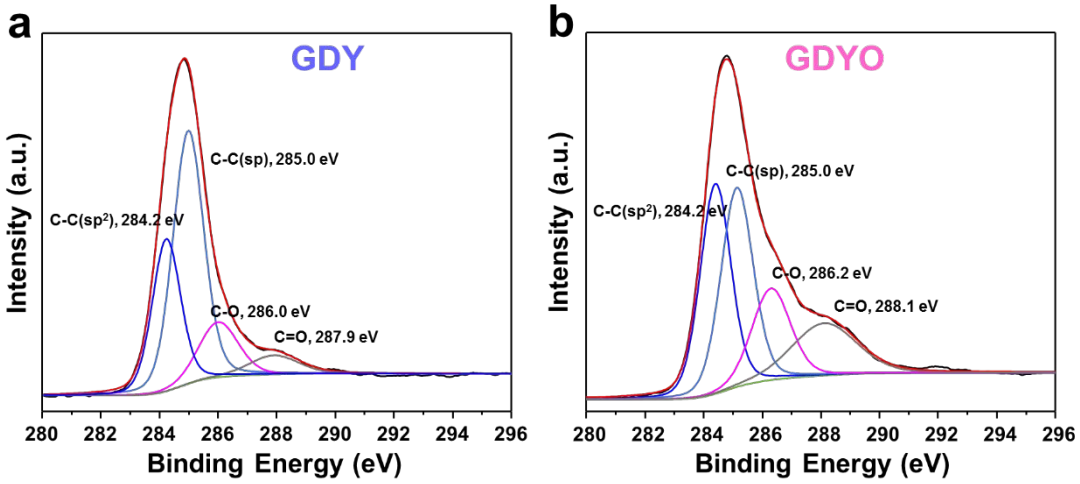


Figure S7. XPS spectra for C 1s of (a) GDY and (b) GDYO nanosheets.

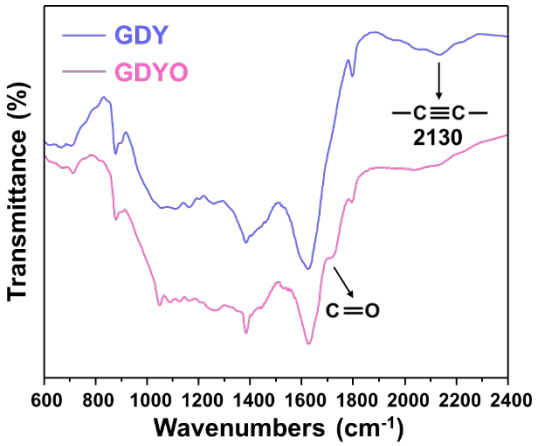


Figure S8. FT-IR spectra of GDY and GDYO nanosheets.

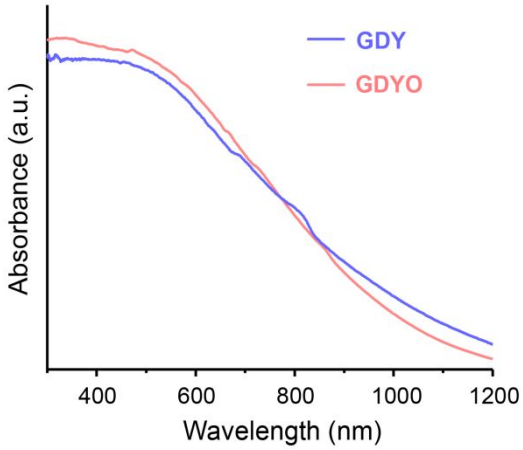


Figure S9. UV-*vis* diffuse reflectance spectra of GDY and GDYO nanosheets.

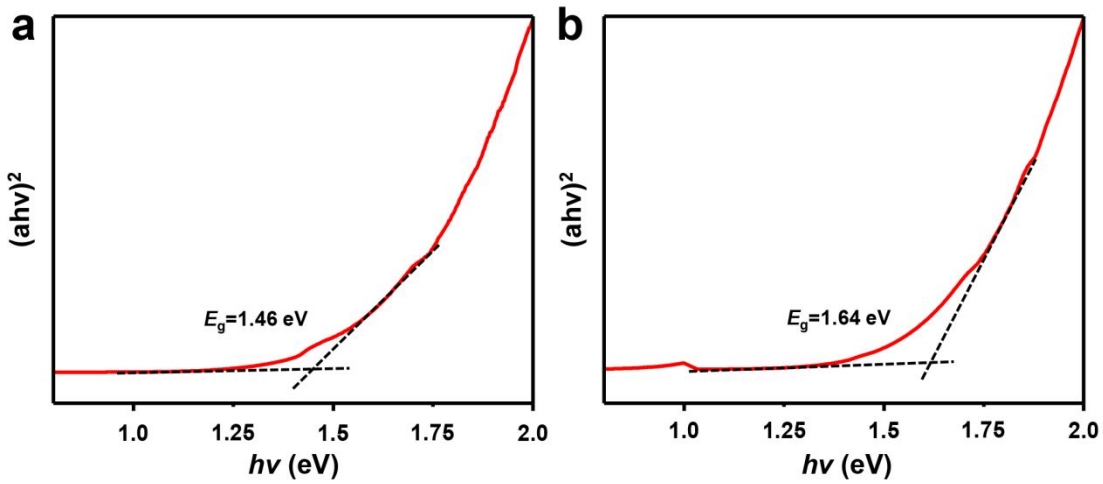


Figure S10. Tauc plots $(\alpha hv)^2$ versus hv curve of (a) GDY and (b) GDYO nanosheets.

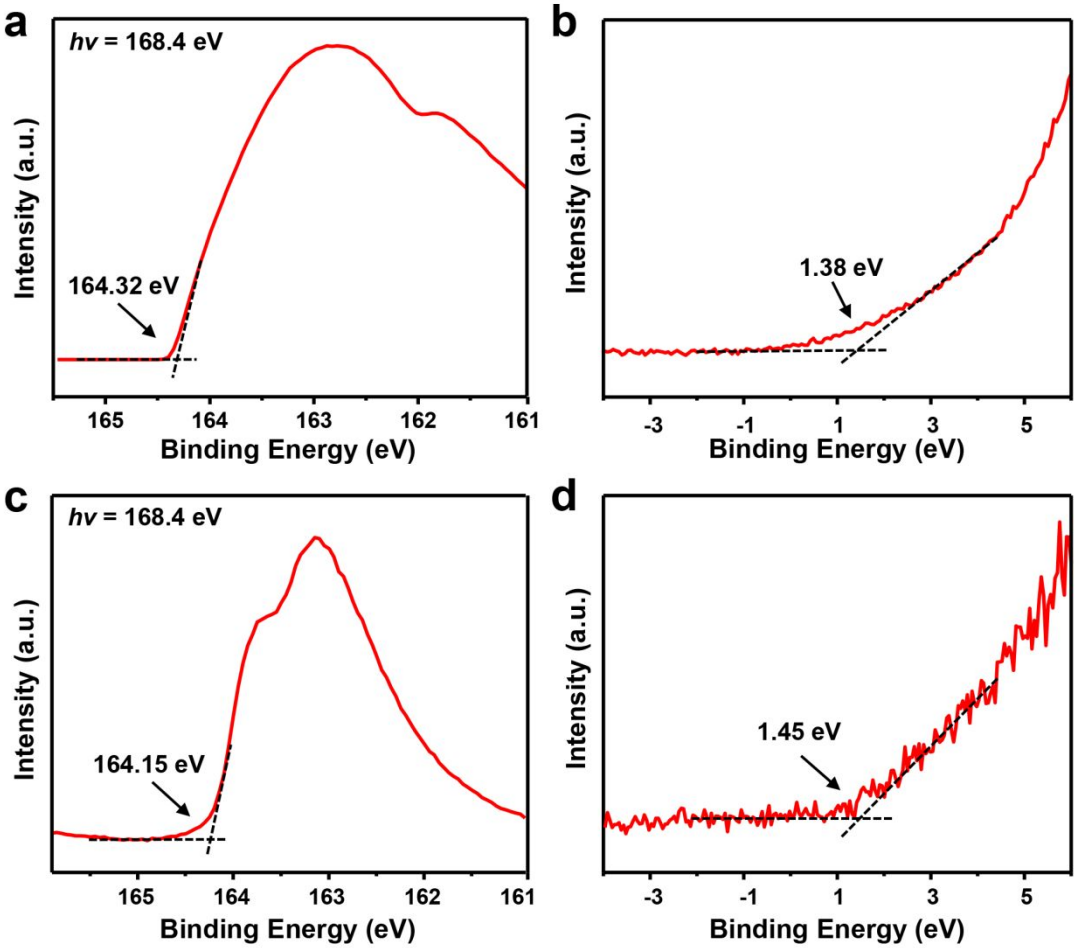


Figure S11. (a, c) Secondary electron cut-off and (b, d) valence band spectra of the GDY and GDYO nanosheets measured by SRPES.

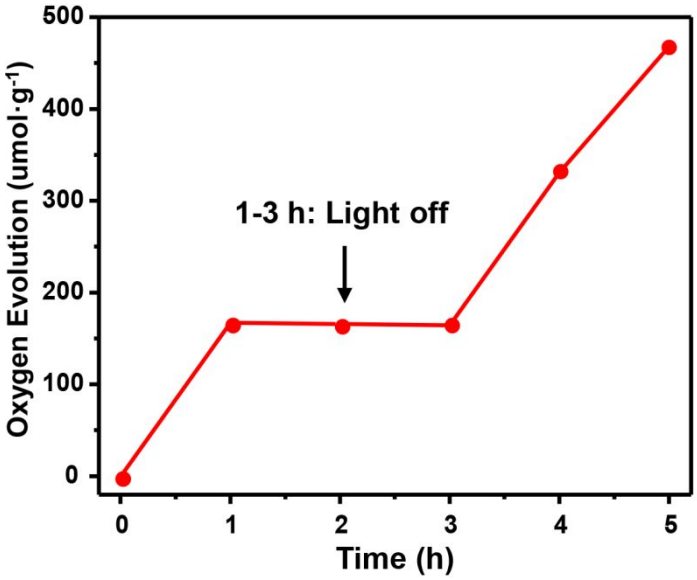


Figure S12. Typical time course of O_2 production under visible light irradiation (λ>420 nm) using GDYO nanosheets photocatalyst. No O_2 could be detected once the light was turned off, indicating the water splitting reaction was initiated by incident photons.

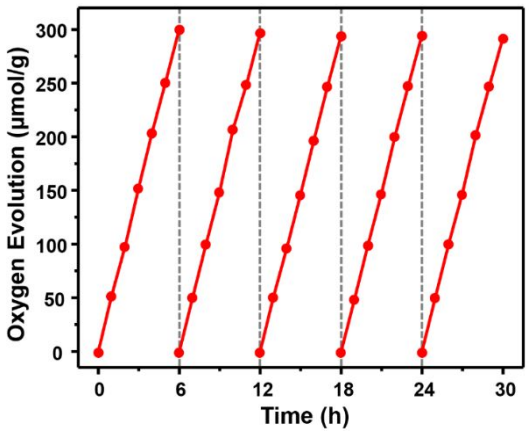


Figure S13. Photocatalytic O_2 evolution of GDYO nanosheets for five consecutive cycles under 660 nm laser irradiation.

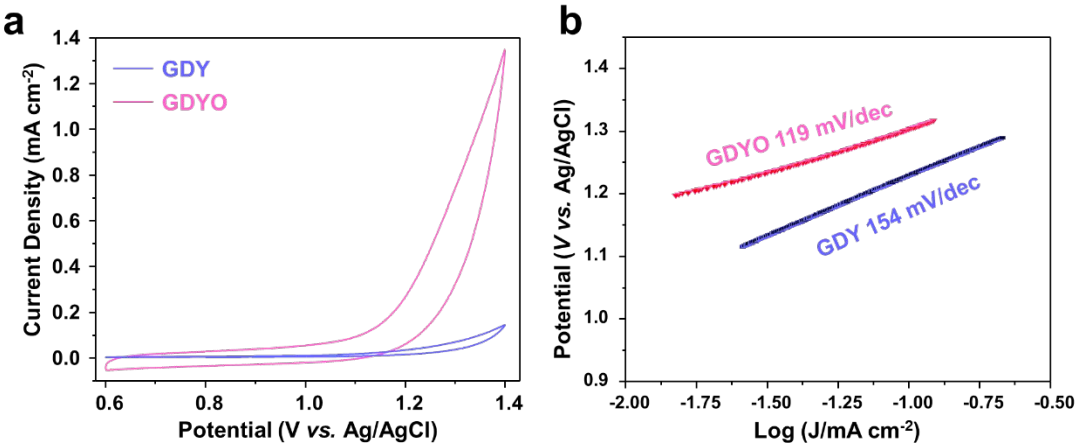


Figure S14. (a) CV curves for OER on GDY and GDYO thin films in 0.1 M phosphate buffer solution under visible light irradiation (λ>420 nm). The scan rate was 50 mV/s. (b) Corresponding Tafel plots for GDY and GDYO nanosheets.

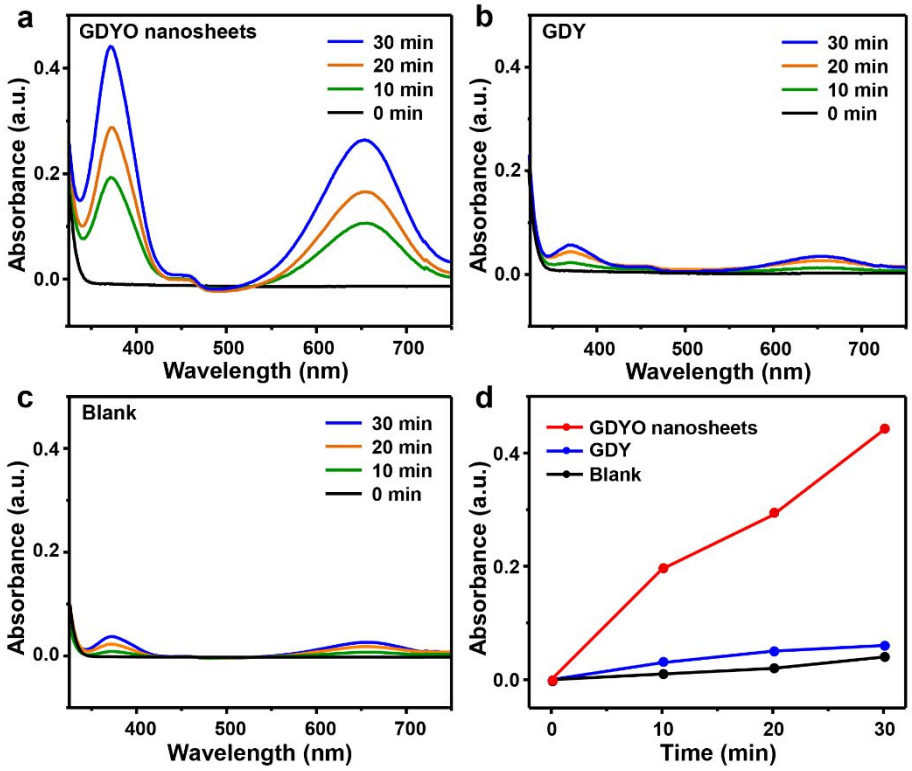


Figure S15. Time-dependent absorption spectra of TMB under visible-light irradiation with different catalysts: (a) GDYO nanosheets, (b) GDY and (c) blank. (d) The optical absorbance of TMB molecule monitored at 380 nm.

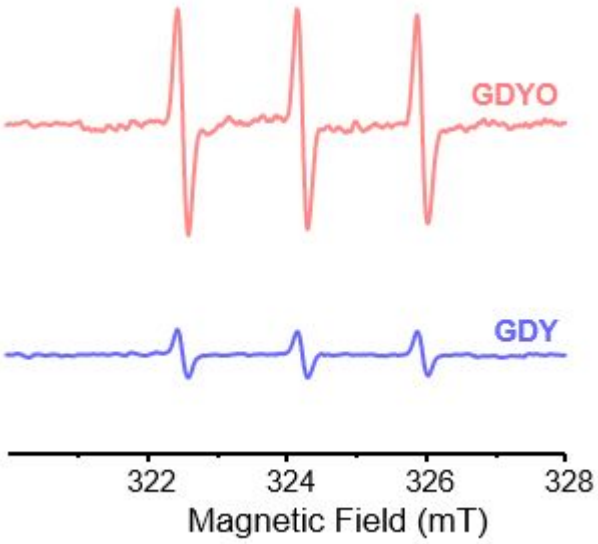


Figure S16. ESR spectra of different samples in the presence of TEMP.

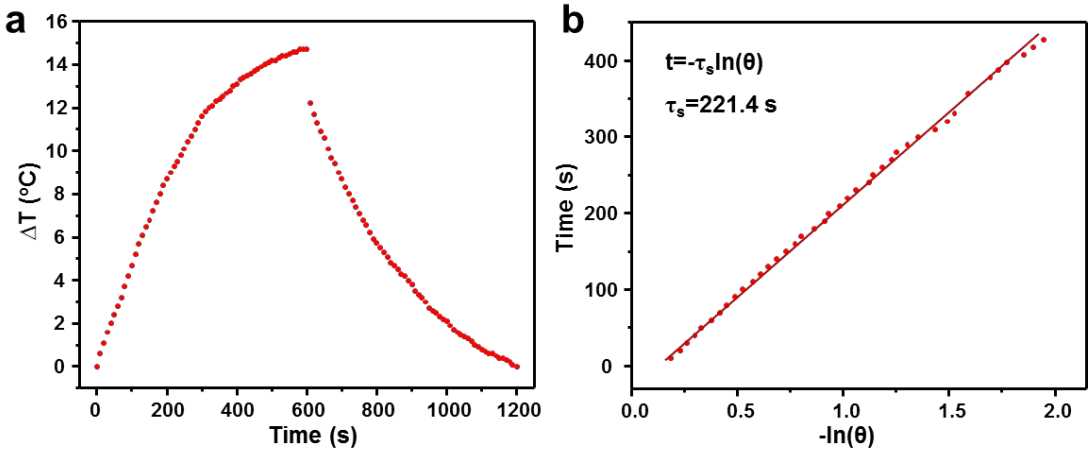


Figure S17. (a) Photothermal response of GDYO aqueous solution irradiated with 660 nm laser (0.5 W/cm^2) for 10 min and then shut off the laser. (b) Plot of time versus negative natural logarithm of the temperature driving force gained from the cooling period.

Figure S18. Photograph of GDYO nanosheets dispersed in different media for 12 h incubation.

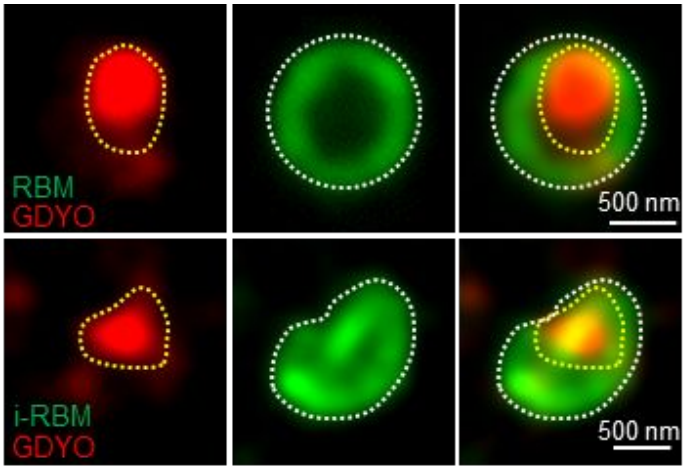


Figure S19. Fluorescence images of GDYO@RBM, GDYO@i-RBM, i-RBM, RBM and GDYO were labeled with FITC-peptide anchors and Cy5 dye, respectively.

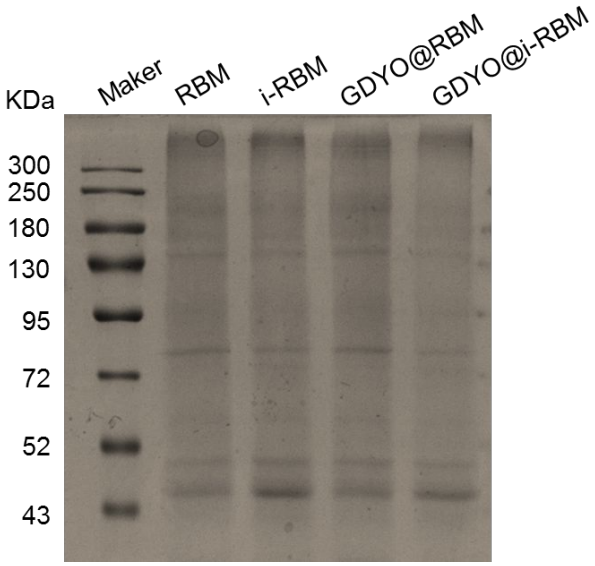


Figure S20. RBM protein retention of GDYO@i-RBM. SDS-PAGE protein analysis in the RBM, i-RBM, GDYO@RBM and GDYO@i-RBM.

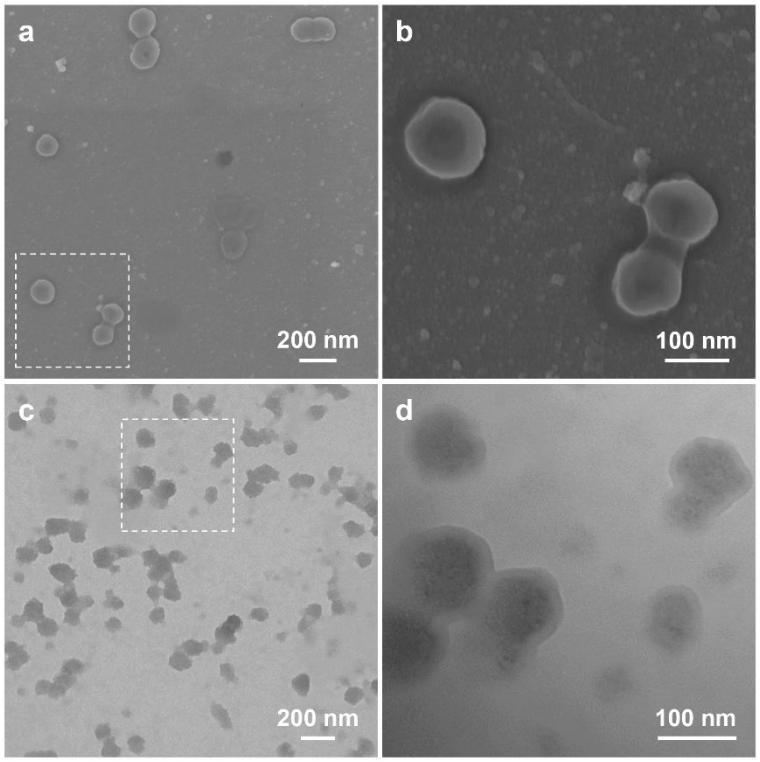


Figure S21. (a, b) SEM and (c, d) TEM images of GDYO@i-RBM.

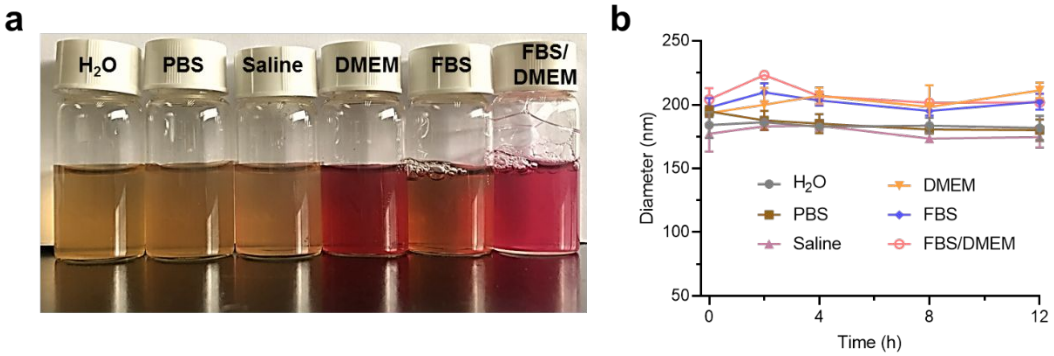


Figure S22. (a) A photo of GDYO@i-RBM nanosheets dispersed in different media for 12 h. (b) The size changes of GDYO@i-RBM nanosheets dispersed in different media.

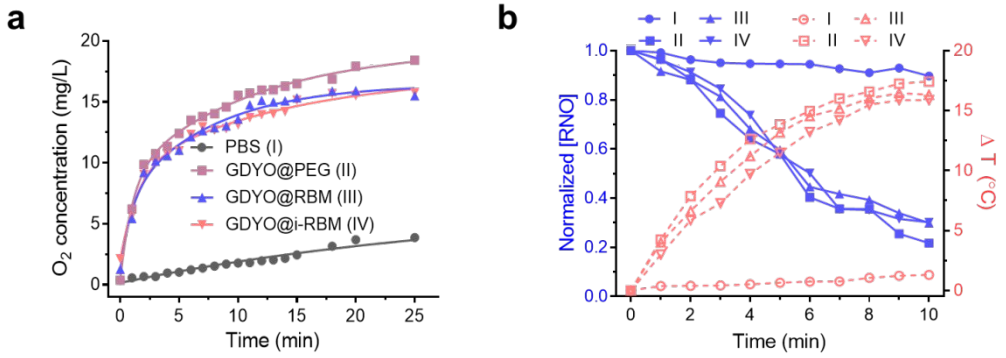


Figure S23. Red blood cell membrane (RBM) modification had no obvious effect on the O_2 generation, photothermal, and photodynamic properties of GDYO nanosheets. (a) Time dependent O_2 evolution of by above formulations at GDYO dose of 50 μg/mL irradiated with a 660 nm laser (0.5 W/cm^2). (b) Normalized absorbance of *N*, *N*-dimethyl-4-nitrosoaniline (RNO) at 440 nm (solid symbols) and temperature changes (empty symbols) by above formulations at GDYO dose of 50 μg/mL irradiated with 660 nm laser (0.5 W/cm^2).

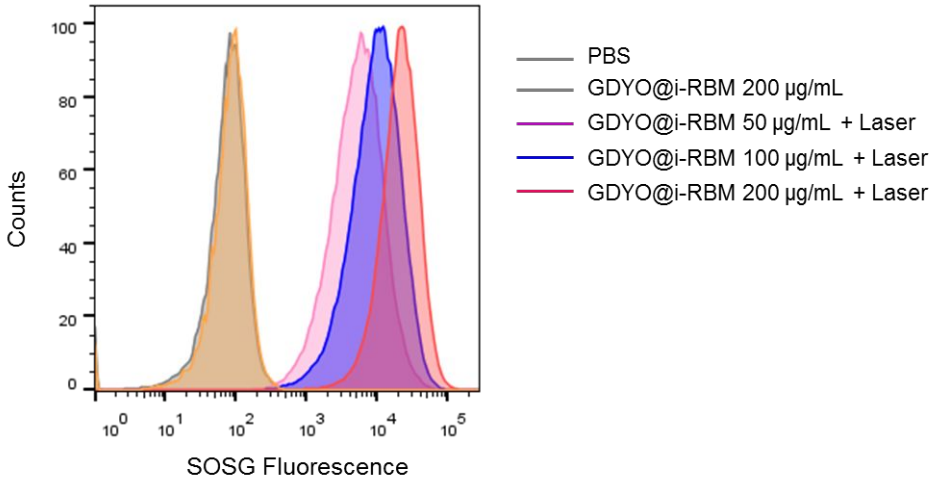


Figure S24. Generation of $^1O_2$ by FACS within EMT-6 cells pre-incubated of various formulations under a hypoxic condition and followed with 660 nm laser irradiation (0.5 W/cm^2, 10 min) using SOSG as the fluorescent probe.

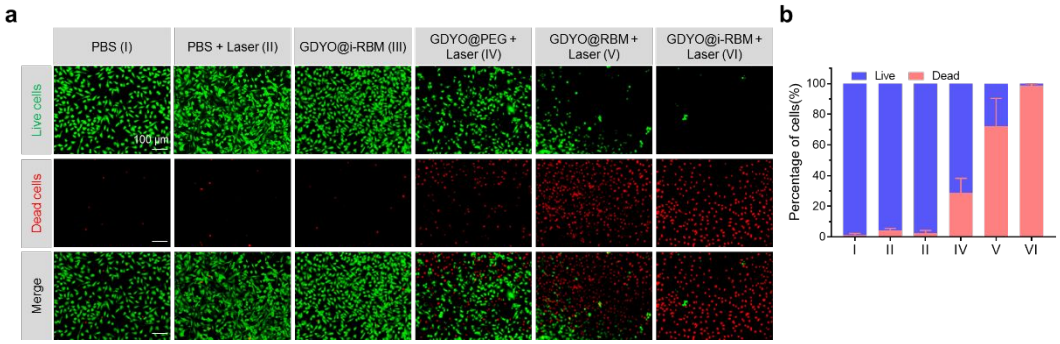


Figure S25. (a) Fluorescence images of calcein AM (green, live cells) and propidium iodide (red, dead cells) costained EMT-6 cells per-treated with GDYO@PEG, GDYO@RBM, and GDYO@i-RBM at GDYO dose of 100 μg/mL with or without laser irradiation (0.5 W/cm^2, 10 min). (b) Corresponding percentage of cells statistics from plane A.

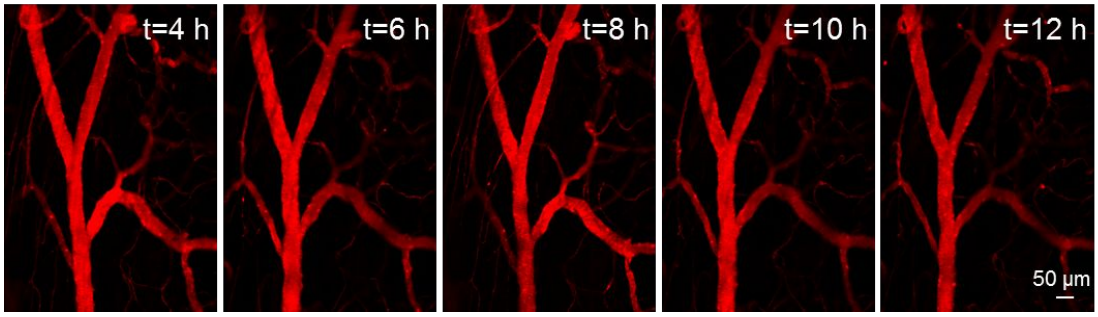


Figure S26. Representative normal skin tissue vascular images captured at different time after *i.v.* injected DiD-labeled GDYO@i-RBM (red).

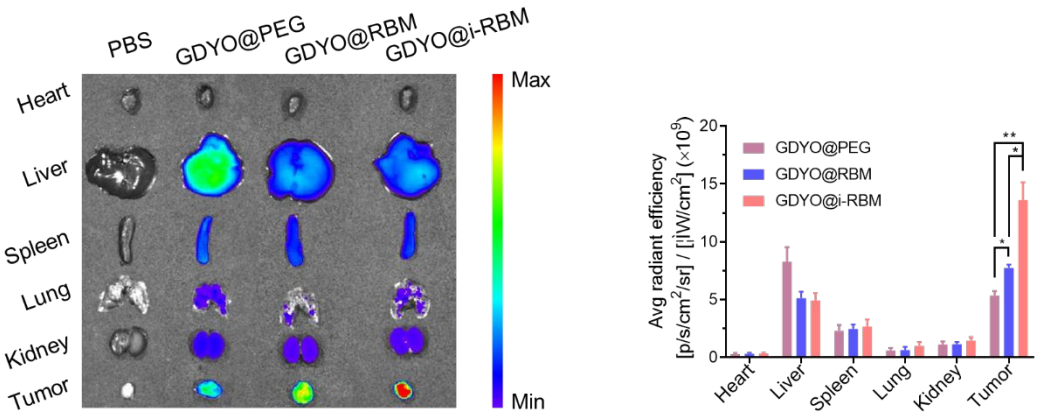


Figure S27. Fluorescence imaging and corresponding intensity of heart, liver, spleen, lung, kidney and tumor of the EMT-6 tumor bearing mice. Images were taken at 96 h post-injection of DiR labeled various formulations (n = 3).

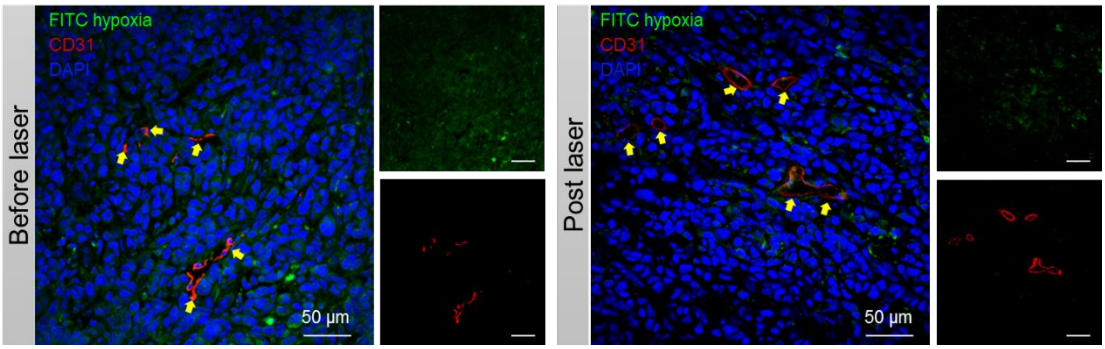


Figure S28. CLSM examination of immunofluorescence and morphometric analyses of the vascular network in EMT-6 tumor before and post laser irradiation. The blood vessels and hypoxia were stained with red fluorescence-stained CD31 antibody, green fluorescence-stained hypoxia region.

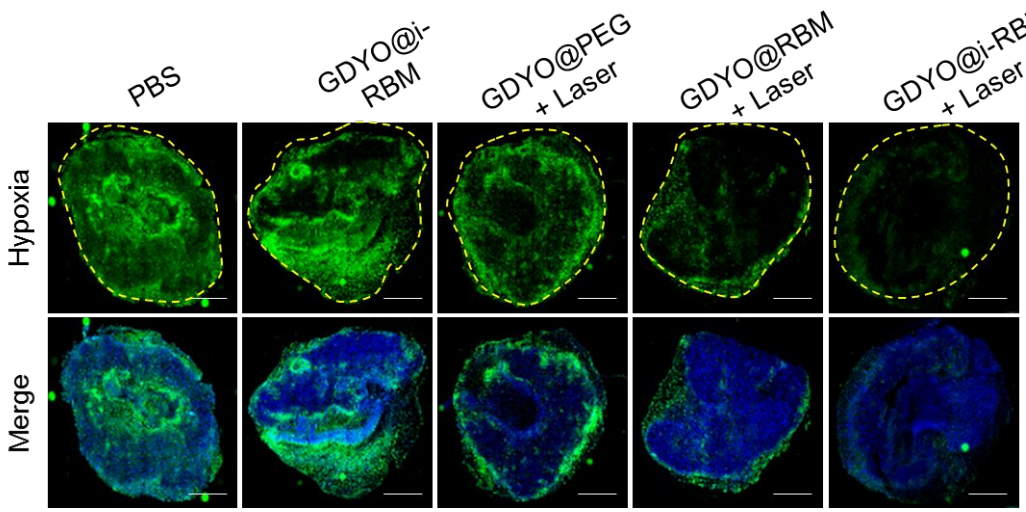


Figure S29. Representative immunofluorescence images of tumor slices stained with hypoxyprobe (green). The yellow dashed lines indicate the tumor boundaries (scale bar = 1 mm).

Table S1. The zeta potential values of GDYO@i-RBM.

	i-RBM	GDYO@PEG	GDYO@i-RBM (GDYO:i-RBM protein w/w)		
			2:1	1:1	1:2
Zeta potential (mV)	-12.3	-20.1	-18.6	-13.2	-13.0

Table S2. Pharmacokinetic parameters of different formulations.

Parameter	GDYO@PEG	GDYO@RBM	GDYO@i-RBM
C_{max} [μg mL^{-1}][a)]	34.07 ± 10.8	89.31 ± 10.58	83.42 ± 28.221
T_{max} [h][b)]	0.083	0.083	0.083
AUC_{0-96h} [μg L^{-1}*h][c)]	833.02 ±63.11	2649.02 ± 94.08	2138.89 ±184.64
$T_{1/2}$ [h][d)]	15.241 ± 5.643	48.15 ± 8.28	42.17 ± 8.89
CLz [L h^{-1} kg^{-1}][e)]	19.32 ± 2.58	5.97 ± 0.43	5.47 ± 1.05

[a)] C_{max}: Peak concentration
[b)] T_{max}: Time at maximum concentration
[c)] AUC_{0-96h}: Area under the curve
[d)] $T_{1/2}$: Terminal elimination half-life time
[e)] CLz: Clearance rate

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[2] G. X. Li, Y. L. Li, H. B. Liu, Y. B. Guo, Y. J. Li, D. B. Zhu, *Chem. Commun.* **2010**, *46*, 3256.

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