



# Host–guest complexation-mediated codelivery of anticancer drug and photosensitizer for cancer photochemotherapy

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Although platinum-based anticancer drugs prevail in cancer treatment, their clinical applications are limited by the severe side effects as well as their ineffectiveness against drug resistant cancers. A precise combination of photodynamic therapy (PDT) and chemotherapy can synergistically improve the therapeutic outcome and thereby may overcome drug resistance through a multipronged assault. Herein, we employ the well-defined cavity of a discrete organoplatinum(II) metallacage (M) to encapsulate octaethylporphine (OEP), a photosensitizer, forming a dual-functionalized system M⊃OEP that is wrapped into the hydrophobic core of the nanoparticles (MNPs) self-assembled from an amphiphilic diblock copolymer. Using a copper-free click reaction, a targeting ligand is conjugated on the surface of the MNPs, aiming to specifically deliver a chemotherapeutic drug and a photosensitizer to cancer cells. Benefiting from the enhanced permeability and retention effect and active targeting capability, high tumor accumulation of MNPs is achieved, leading to an improved therapeutic outcome and reduced side effects. In vivo studies demonstrate that the combination of chemotherapy and PDT exhibits a superior antitumor performance against a drug-resistant tumor model attributed to their synergistic anticancer efficacy.

supramolecular coordination complex | metallacage | photodynamic therapy | theranostic | drug delivery

Platinum-based drugs including cisplatin, carboplatin, and oxaliplatin are used worldwide in cancer treatment; however, their dose-limiting side effects arising from the poor selectivity to cancerous tissue over normal tissues always cause serious complications in patients (1–5). Considerable attention has been given to the development of smart drug-delivery systems that can temporarily passivate platinum complexes and specifically transport the nanomedicines to tumor sites via the enhanced permeability and retention (EPR) effect (6–8). Various nanocarriers including liposomes, micelles, and dendrimers have been employed that can selectively transport platinum-based anticancer drugs to cancerous cells (9–11), while the clinical use of these nanomedicines is still limited by drug resistance, including inherent and acquired resistance, promoting researchers to combine chemotherapy with other treatment modalities to achieve synergetic anticancer efficacy through a multipronged assault (12–15).

Photodynamic therapy (PDT) employs photosensitizers that upon absorbing a specific wavelength of light to release a cell-damaging version of reactive oxygen species (singlet oxygen, <sup>1</sup>O<sub>2</sub>) that can eradicate tumors with a high specificity and negligible side effects (16–18). The sensitization effect of PDT can significantly boost the activity of chemotherapeutic agents, synergistically overcoming drug resistance through different mechanisms of actions to realize enhanced anticancer efficacy (19–22). However, the full promise of PDT has not yet been achieved mainly due to the lack of ideal photosensitizers and sophisticated delivery/activation processes. Many existing photosensitizers, such as phthalocyanine, porphyrin,

bacteriochlorin derivatives, and boron dipyrromethene dyes, are conjugated molecules with poor water solubility and exhibit serious aggregation tendency under physiological conditions, both of which lower the PDT efficacy (23, 24). Moreover, the suboptimal tumor accumulation of the photosensitizers after systemic administration also reduces the efficacy of PDT in clinical use.

To overcome these issues, we utilize a discrete organoplatinum(II) metallacage (M) to complex a photosensitizer [octaethylporphine (OEP)] through noncovalent interactions (Fig. 1). *Cis*-(PEt<sub>3</sub>)<sub>2</sub>Pt(OTf)<sub>2</sub> (cPt), a chemotherapeutic agent, is employed as the corners of the metallacage such that the host–guest complex M⊃OEP can act as a dual functionalized system to achieve synergistic anticancer efficacy. The solubility and stability of M⊃OEP in a physiological environment are improved by wrapping it into the hydrophobic core of an amphiphilic diblock copolymer (N<sub>3</sub>-PEG-*b*-PLBG), resulting in the formation of nanoparticles (MNPs) having azide groups on the surface for further incorporating a targeting ligand (cRGDfK) via an in situ

## Significance

The combination of chemotherapy and photodynamic therapy opens up a promising way of overcoming drug resistance, incorporating different mechanisms of actions to achieve synergistic efficacy. However, the antitumor outcome of photodynamic therapy is greatly limited due to the unsatisfactory singlet oxygen generation caused by severe aggregation of the photosensitizer. To this end, we utilize a discrete metallacage containing therapeutic organoplatinum(II) to encapsulate a photosensitizer by forming an inclusion host–guest complex, facilitating the codelivery of chemotherapeutic agent and photosensitizer through nanoformulation. Benefiting from the enhanced permeability and retention effect and active targeting, the nanomedicine exhibits satisfactory antitumor performance against drug-resistant tumor. This pioneering work provides a distinct supramolecular methodology to prepare theranostic systems for multimodality imaging and therapy.

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copper-free click reaction. Benefiting from these rational designs, high tumor accumulation and cellular internalization of **MNPs** are realized, which are beneficial to improve the therapeutic results while reducing the systemic toxicity. In vivo studies demonstrate that **MNPs** hold superior anticancer ability to overcome drug resistance, effectively suppressing tumor growth by combining chemotherapy and PDT.

## Results and Discussion

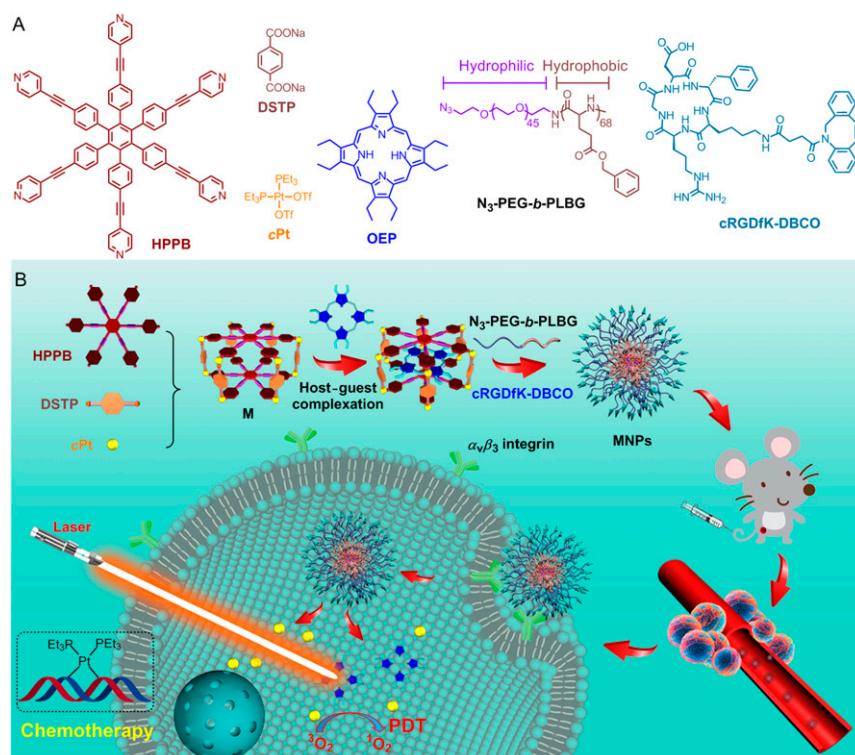
Using a multicomponent coordination self-assembly approach, **M** was quantitatively prepared from a total of 20 molecular components from three unique species, including hexakis[4-(4-pyridylethynyl)phenyl]benzene (**HPPB**), disodium terephthalate (**DSTP**), and **cPt**, in a 2:6:12 ratio, respectively (Fig. 1A). The successful construction of **M** was verified by  $^1\text{H}$  NMR and  $^{31}\text{P}\{^1\text{H}\}$  NMR spectroscopies. Well-defined signals were observed for the protons of **M** in the  $^1\text{H}$  NMR spectrum (*SI Appendix*, Fig. S3), suggesting that the resultant species possessed a discrete and highly symmetric structure (25–28). Compared with free **HPPB**, the  $^1\text{H}$  NMR signals related to the pyridyl protons ( $\text{H}_1$  and  $\text{H}_2$ ) shifted downfield upon formation of **M** due to the  $\text{Pt(II)}\leftarrow\text{pyridine}$  coordination interactions (*SI Appendix*, Fig. S3), while the peaks corresponding to the protons  $\text{H}_3$  and  $\text{H}_4$  shifted upfield. Attributed to the heterologation-directed coordinations between  $\text{Pt(II)}\leftarrow\text{pyridine}$  and  $\text{Pt(II)}\leftarrow\text{carboxylate}$ , the single peak of **cPt** in  $^{31}\text{P}\{^1\text{H}\}$  spectrum split into two different doublets after coordination (Fig. 2A and B), further confirming the putative structure of a discrete metallacage.

The host–guest complexation between **M** and **OEP** was confirmed by the  $^{31}\text{P}\{^1\text{H}\}$  spectrum, in which significant downfield shifts (from 5.13 and  $-0.33$  ppm to 8.49 and 3.03 ppm, respectively) were observed after the addition of **OEP** into the solution of **M** (Fig. 2C). Additionally, the host–guest interactions were examined by molecular modeling,  $^1\text{H}$  NMR, ultraviolet and visible (UV-vis), and fluorescence spectroscopies (*SI Appendix*,

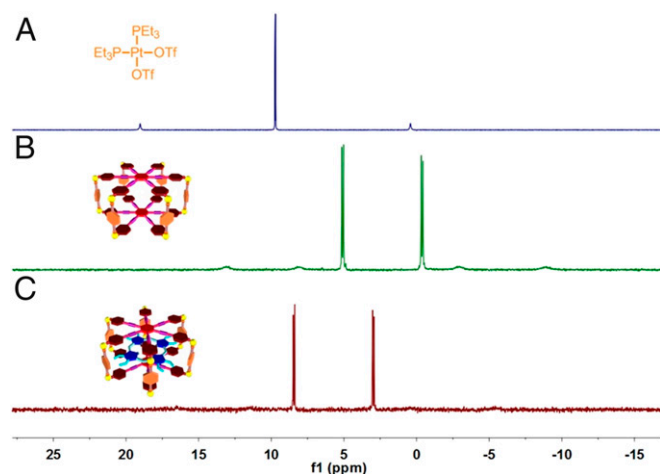
Figs. S4–S8). From the  $^1\text{H}$  NMR titration data, the association constant was calculated to be  $(4.91 \pm 0.36) \times 10^4 \text{ M}^{-1}$  with a 1:1 stoichiometry using a nonlinear curve-fitting method (*SI Appendix*, Figs. S9–S12). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) demonstrated that free **OEP** molecules could stack into the nanofibers that were transformed into irregular aggregates in aqueous solution upon addition of **M** (*SI Appendix*, Fig. S13). These studies revealed that the  $\pi$ - $\pi$  stacking interactions among the free **OEP** molecules were greatly inhibited after the host–guest complexation, indicating that the photosensitizer could be well dispersed via the supramolecular strategy.

For biomedical applications, the stability and solubility of **M** and **OEP** need to be further improved. Hence, **N<sub>3</sub>-PEG-*b*-PLBG** was utilized as a polymeric shield that encapsulated **M** and **OEP** into its hydrophobic core and provided **MNPs** consisting of 30.6% **M** and **OEP** (*SI Appendix*, Table S1). To endow the nanoparticles with a targeting capability toward the  $\alpha_v\beta_3$  integrin overexpressing cancer cells, cyclic RGD (cRGDfK) functionality was attached on the surface of **MNPs** via a copper-free click reaction between cRGDfK-DBCO and the azide groups of the polymeric shield. The resultant functionalized nanoparticles were characterized by a suite of analytical techniques. For example, dynamic light scattering (DLS) measurement indicated that the average diameter of **MNPs** was  $109 \pm 8.4 \text{ nm}$  (*SI Appendix*, Figs. S14 and S15), which was in accordance with their TEM data (Fig. 3A). The zeta potential of **MNPs** was determined to be  $3.45 \pm 0.21 \text{ mV}$  (*SI Appendix*, Fig. S16). DLS was further employed to examine the stability of **MNPs** in a physiologic environment, the results showed a negligible change in the average diameter of **MNPs** even after its incubation in PBS containing 10% FBS for over 72 h (*SI Appendix*, Fig. S17). The PEG segments in **MNPs** likely provided a neutral shell to inhibit the absorption by proteins during the delivery process (29, 30).

The release behaviors of **cPt** and **OEP** from the **MNPs** were studied using inductively coupled plasma mass spectrometry (ICP-MS) and UV-vis spectroscopy under different conditions.



**Fig. 1.** (A) Chemical structures of **HPPB**, **DSTP**, **cPt**, **OEP**, **N<sub>3</sub>-PEG-*b*-PLBG**, and **cRGDfK-DBCO**. (B) Cartoon illustration of the preparation of **MNPs** and their photochemotherapy, followed by the tumor accumulation through EPR effect and receptor-mediated internalization.



**Fig. 2.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra (121.4 MHz,  $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{CN} = 1/1$ , 298 K) of **cPt** (A), **M** (B), and **M $\Delta$ OEP** (C).

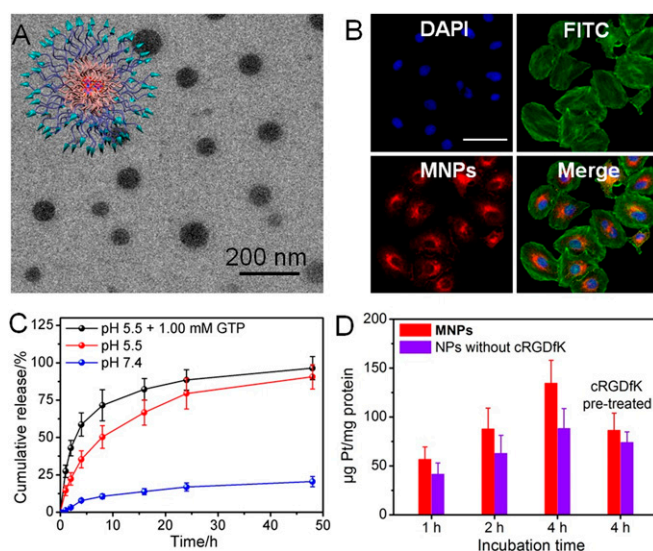
As illustrated in Fig. 3C, the release curve depicted a slow and sustained manner at pH 7.4, with a plateau of a total of 20.5% platinum released over 48 h, indicating that these **MNPs** were fairly stable under physiological conditions. The release was accelerated at pH 5.5, likely due to the dissociation of the metallacages under acidic condition by protonating the pyridine and carboxylate groups, which was beneficial for drug release after being internalized by cancer cells. A substantially faster and more profound release of **cPt** was observed when the **MNPs** were incubated in the presence of GTP at pH 5.5, in which ca. 96% of **cPt** was released from the **MNPs** within 48 h. This likely indicated that the coordination interactions between the  $\text{N}_7$  atoms of guanosine and the platinum centers facilitated the dissociation of the metallacage (31, 32). **OEP** could also escape from **MNPs**; however, its release rate was slower than that of **cPt** under the same conditions, possibly resulting from its relatively low diffusion ability (SI Appendix, Fig. S18). These studies demonstrated that the chemotherapeutic drug and photosensitizer could be released in lysosomes/endosomes, predicting that the photochemotherapy may synergistically work inside cancer cells.

The cellular internalization of **MNPs** was studied using confocal microscopy (CLSM) and ICP-MS. As shown in Fig. 3B, a red fluorescence of **OEP** was observed in cytoplasm after the cells were incubated with **MNPs** for 8 h. The intracellular red fluorescence was greatly weakened by pretreating A2780CIS cells with free cRGDFK (SI Appendix, Fig. S19), demonstrating that the existence of targeting ligands on the surface of **MNPs** was favorable for their receptor-mediated uptake. ICP-MS results further indicated that the uptake of **MNPs** by A2780CIS cells was time-dependent (Fig. 3D); the intracellular platinum content increased by extending the incubation time. For example, the intracellular platinum content increased from 56.8 to 135 ng Pt/mg protein when the incubation time was extended from 1 to 4 h. Similarly, the internalization of **MNPs** was blocked when the receptors were occupied by pretreating the cells with free cRGDFK. The intracellular Pt content in A2780CIS cells cultured with NPs formed from **M $\Delta$ OEP** and **N<sub>3</sub>-PEG-*b*-PLBG**, i.e., without including the targeting groups, was much lower than that of **MNPs** under the same conditions, further confirming that the presence of targeting ligands facilitated the cellular internalization of **MNPs**.

Singlet oxygen sensor green (SOSG), a highly selective  $^1\text{O}_2$  probe, was utilized to detect the generation of  $^1\text{O}_2$  by **MNPs** upon laser irradiation of a solution containing SOSG and **MNPs**. The characteristic peak at 532 nm rapidly increased (Fig. 4A), because the SOSG in silent form was oxidized by the generated  $^1\text{O}_2$ . Likewise, in the UV-vis spectrum of a solution containing

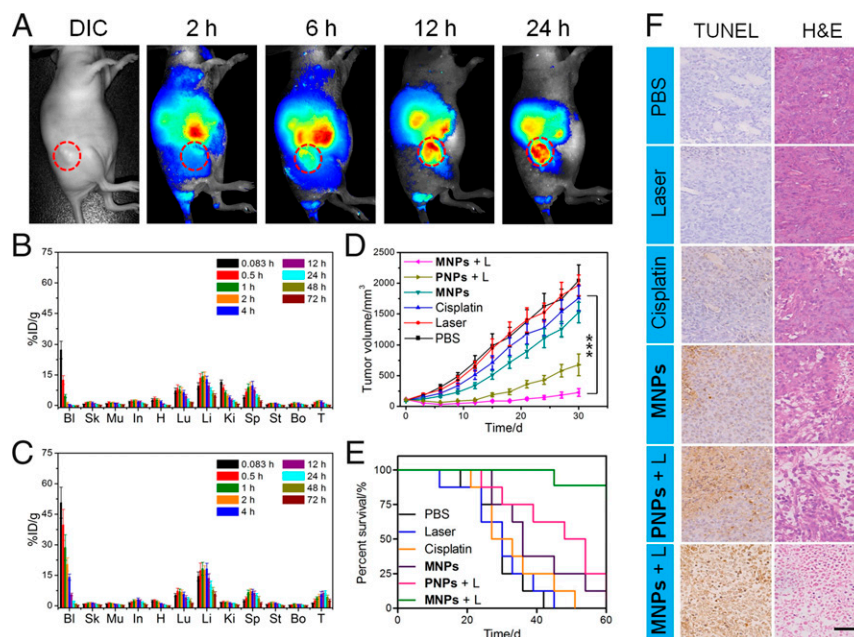
anthracene-9,10-dipropionic acid disodium (ADPA) and **MNPs**, all of the diagnostic absorption bands (340–450 nm) of ADPA were gradually decreased upon irradiation, which confirmed the oxidation of ADPA by  $^1\text{O}_2$  (Fig. 4B). In contrast, negligible changes in ADPA's absorptions were noticed when **OEP** was employed as a photosensitizer, suggesting that the aggregation of **OEP** in aqueous solution was responsible for this negative outcome (SI Appendix, Figs. S20 and S21). This difference emphasized that the host-guest complexation and nanoformulation greatly improved the photodynamic effect of **OEP**. The intracellular  $^1\text{O}_2$  generation by **MNPs** was evaluated using dichlorofluorescein diacetate (DCF-DA) as an oxidant-sensitive fluorescent dye, which was nonfluorescent in its original state but became highly emissive after being oxidized into dichlorofluorescein (DCF). CLSM images showed that the strong green fluorescence of DCF was observed in the cytoplasm of A2780CIS cells cultured with **MNPs** followed by irradiation, a direct evidence for the efficient generation of  $^1\text{O}_2$  inside the cells (Fig. 4G and H). In a control experiment, vitamin C was employed as a  $^1\text{O}_2$  scavenger that could deplete the intracellular  $^1\text{O}_2$  originating from the photodynamic effect. Fig. 4I indicated that the green fluorescence significantly diminished by pretreating the cells with vitamin C (50.0  $\mu\text{M}$ ), further confirming the effective  $^1\text{O}_2$  production by **MNPs** under laser irradiation. Flow cytometry was also utilized to monitor the intracellular generation and scavenging of  $^1\text{O}_2$  by probing the green fluorescence of DCF (Fig. 4J–L); the data were in good agreement with the CLSM images.

A 3-(4',5'-dimethylthiazol-2'-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay was used to assess the synergistic anticancer efficacy of the photochemotherapy. Cisplatin and **OEP**-loaded NPs (**PNPs**) were used as controls for the chemotherapy and PDT, respectively. For A2780 cells, the  $\text{IC}_{50}$  values of cisplatin, **cPt**, **MNPs**, and **PNPs**, followed by laser irradiation (**PNPs** + L), and **MNPs**, followed by irradiation (**MNPs** + L) were measured to be  $2.53 \pm 0.16$ ,  $3.57 \pm 0.28$ ,  $1.32 \pm 0.10$ ,  $1.05 \pm 0.08$ , and  $0.39 \pm 0.04$   $\mu\text{M}$ , respectively (Fig. 4C). The combination index (CI) was calculated to be 0.67, which was lower than 1, indicating a synergistic effect was realized for the **MNPs** by combining PDT and chemotherapy. Due to the drug resistance, the  $\text{IC}_{50}$  values against



**Fig. 3.** (A) TEM image of **MNPs**. (B) CLSM image of A2780CIS cells treated with **MNPs**. Blue fluorescence is from the nucleus stained with DAPI, green fluorescence is from the  $\beta$ -actin stained with FITC, and red fluorescence is from **MNPs**. (Scale bars: 25  $\mu\text{m}$ .) (C) Release behaviors of the platinum-based drug under different conditions. (D) Time-dependent internalization of **MNPs** or NPs without cRGDFK by A2780CIS cells.





**Fig. 5.** (A) Time-dependent fluorescence images of A2780CIS tumor-bearing mouse after i.v. injection of MNPs. Tissue distributions of cisplatin (B) and MNPs (C) at different time post-i.v. injection. Bl, blood; Bo, bone; H, heart; In, intestine; K, kidney; Li, liver; Lu, lung; Mu, muscle; Sk, skin; Sp, spleen; St, stomach; T, tumor. (D and E) Tumor growth inhibition curves (D) and survival rate (E) of the mice bearing A2780CIS tumors after different treatments ( $n = 8$ ).  $***P < 0.001$ . (F) TUNEL and H&E staining of the tumor tissues from the mice treated with different formulations. (Scale bar: 200  $\mu\text{m}$ .)

biodistribution of MNPs in the main organs and tumors was quantitatively analyzed by ICP-MS. As a low-molecular-weight drug, cisplatin entered the organs rapidly; the maximum platinum level in each organ was observed within 2 h after i.v. injection (Fig. 5B). Due to its fast clearance, the platinum amount accumulated in the tumor tissues was low, the highest platinum concentration in the tumor was  $1.93 \pm 0.34\% \text{ID/g}$  (percentage injected dose/gram tissue) at 2 h postinjection. It should be noted that the drug was eliminated from the body mainly through a renal excretion pathway. This was supported by the fact that a high platinum level was monitored in the kidney at the first 2 h, which was likely responsible for its severe nephrotoxicity. For the mice treated with MNPs, the Pt amount in the tumor gradually increased to  $6.47 \pm 0.92\% \text{ID/g}$  at 24 h postinjection (Fig. 5C), which was 10.8-fold higher than that of the cisplatin-treated group ( $0.60 \pm 0.09\% \text{ID/g}$ ). The intratumoral platinum level was maintained at a relatively high level ( $2.73 \pm 0.41\% \text{ID/g}$ ) even after 72 h postinjection. Due to the prolonged blood circulation time, a high accumulation of MNPs was monitored in the reticuloendothelial system, such as the liver and spleen, which was common in most nanomedicines. Additionally, the employment of nanoparticles as drug-delivery carriers reduced the platinum level in the kidney, greatly avoiding the renal toxicity of platinum-based anticancer drugs.

The in vivo antitumor performance of the photochemotherapy was evaluated using A2780CIS tumor-bearing nude mice. As shown in Fig. 5D, no influence on the tumor growth was observed by the laser irradiation, as verified by the tumors' rapid growth. Compared with the control group administrated with PBS, limited therapeutic results were observed for the mice that received a single chemotherapy (cisplatin and MNPs), because the drug-resistant tumor model was insensitive to chemotherapy. Due to the EPR effect and targeting capability, a relatively higher antitumor efficacy was realized for the mice treated with MNPs than those administrated with cisplatin. For PDT alone (PNPs + L), an effective tumor growth inhibition was achieved in the first 12 d. However, a tumor recurrence appeared afterward, because the infiltrating cancer cells far away from the primary tumor were hardly cleared by a single PDT. The inhibition ratio was calculated to be 14.1%, 25.5%, and 66.8% for the

mice administrated with cisplatin, MNPs, and PNPs + L, respectively (SI Appendix, Fig. S23). A superior antitumor outcome was achieved for the mice receiving photochemotherapy, in which the tumor inhibition rate reached 89.2%. H&E staining demonstrated that the photochemotherapy caused the highest level of apoptosis and necrosis in tumor tissues (Fig. 5F). Furthermore, TUNEL staining showed that photochemotherapy resulted in 93.8% cell apoptosis in tumor sites, which was much higher than the other formulations (Fig. 5F and SI Appendix, Fig. S24), thereby confirming the synergistic anticancer efficacy of MNPs.

During the therapeutic period, the changes in body weight were monitored to assess the systemic toxicity of each formulation. Due to the nonspecific distribution of cisplatin, the administration led to a serious weight loss after three injections (SI Appendix, Fig. S25). The systemic toxicity of cPt was greatly avoided by incorporating the drug into the nanomedicine. Negligible body weight reduction was observed during the therapy period for the mice treated with MNPs or MNPs + L. Moreover, no obvious signs of toxic effects, such as eating, drinking, activity, grooming, urination, or neurological status occurred. The low toxicity of MNPs + L was further evaluated by H&E staining of the main organs (SI Appendix, Fig. S26), in which no observable inflammatory lesions and tissue damages were detected. The median survival rate of the mice treated with PBS, laser, cisplatin, MNPs, and PNPs + L was determined to be 28, 29, 31, 36, and 51 d, respectively, whereas the survival rate extended over 60 d for the mice that received photochemotherapy (Fig. 5E). Moreover, in vivo blood biochemistry test demonstrated that the hepatotoxicity and nephrotoxicity of the platinum-based anticancer drug were significantly inhibited through nanoformulations (SI Appendix, Fig. S27). Routine blood analysis indicated that the levels of the biomarkers were in the normal range (SI Appendix, Fig. S28), and a negligible difference was found between the healthy mice and the mice treated with photochemotherapy.

## Conclusion

In summary, a discrete organoplatinum(II) metallacage **M** containing a platinum-based anticancer drug was employed to encapsulate a photosensitizer (OEP) through noncovalent interactions. The

host-guest complex was further wrapped up by an amphiphilic copolymer, resulting in the formation of MNPs with the capability to codeliver a chemotherapeutic agent and a photosensitizer. The targeting ligand was introduced through an in situ copper-free click reaction, endowing the formed MNPs with the ability to specifically deliver cPt and OEP to cancer cells overexpressing  $\alpha_v\beta_3$  integrin. The MNPs were highly accumulated in the tumor sites benefiting from the EPR effect and active targeting, which were favorable to enhance the therapeutic outcome and reduce side effects. In vivo studies demonstrated that MNPs exhibited a superior antitumor performance on a drug-resistant tumor model by combining chemotherapy and PDT. This work demonstrates a strategy for delivering multiple therapeutic agents/diagnostic probes through supramolecular chemistry that can be useful in treating many difficult-to-treat cancers including drug resistance and thereby possessing promising potentials in cancer theranostics.

## Materials and Methods

Azide-PEG-amine ( $N_3$ -PEG-NH<sub>2</sub>, 2k) was purchased from Biochempeg. Triphosgene, L-glutamic acid,  $\gamma$ -benzyl ester, and other reagents were purchased from Sigma-Aldrich and used as received. Solvents were either employed as purchased or dried according to procedures described in the literature. <sup>1</sup>H NMR and <sup>31</sup>P NMR spectra were recorded on a Bruker Avance

III-300 or 400 spectrometer. <sup>31</sup>P{<sup>1</sup>H} NMR chemical shifts are referenced to an external unlocked sample of 85% H<sub>3</sub>PO<sub>4</sub>. UV-vis spectra were taken on a Shimadzu UV-3150 spectrophotometer. TEM investigations were carried out on a Hitachi HT7700 instrument. The fluorescence experiments were conducted on a RF-5301 spectrofluorophotometer (Shimadzu Corporation). DLS measurements were carried out using a 200-mW polarized laser source Nd:YAG ( $\lambda = 532$  nm). The polarized scattered light was collected at 90° in a self-beating mode with a Hamamatsu R942/02 photomultiplier. The signals were sent to a Malvern 4700 submicrometer particle analyzer system. Molecular weights and distributions were determined by gel permeation chromatography with a Waters 1515 pump and Waters 1515 differential refractive index detector (set at 30 °C).

All experiments involving live animals were approved by the Zhejiang University Animal Care and Use Committee. The details of the synthesis and characterization are given in *SI Appendix*.

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