The development of sophisticated theranostic systems for simultaneous near infrared (NIR) fluorescence imaging and phototherapy is of particular interest. Herein, anisotropic plasmonic metal heterostructures, Pt end-deposited Au nanorods (PEA NRs), are developed to efficiently produce hot electrons under 808 nm laser irradiation, exhibiting the strong electric density. These hot electrons can release the heat through electron-phonon relaxation and form reactive oxygen species through chemical transformation, as a result of potent photothermal and photodynamic performance. Simultaneously, the confined electromagnetic field of PEA NRs can transfer energy to adjacent polyethylene glycol (PEG)-linked NIR fluorophores (CF) based on their energy overlap mechanism, leading to remarkable NIR fluorescence amplification in CF-PEA NRs. Various PEG linkers (1, 3.4, 5.0, and 10 kD) are employed to regulate the distance between CF and PEA NRs of CF-PEA NRs, and the maximum fluorescence intensity is achieved in CF_{5k}-PEA NRs. After further attachment with i-motif DNA/Nrf2 siRNA chimera to simultaneously suppress both cellular antioxidant defense and hyperthermia resistance effects, the final biocompatible CF_{5k}-bPEA@siRNA NRs present promising NIR fluorescence imaging ability and 808 nm laser-activated photothermal and photodynamic therapeutic effect in MCF7 cells and tumor-bearing mice, holding great potential for cancer therapy.
Anisotropic plasmonic metal heterostructures are emerging as potent theranostic platforms to improve the fluorescence imaging and phototherapeutic effect of cancer based on their unique electronic properties. It has been known that localized surface plasmon resonance (LSPR) excited by the incident light can extremely promote the electromagnetic field enhancement and energetic charge carrier generation in plasmonic nanostructures. On one hand, the enhanced electromagnetic field can transfer energy to the fluorophore that is located in close proximity to plasmonic nanostructures, leading to significantly amplified fluorescence intensity of fluorophore when the LSPR band of plasmonic nanostructures overlaps with the fluorophore’s absorption or emission band and the distance between plasmonic nanostructures and fluorophores is appropriate (Scheme S1, Supporting Information). On the other hand, the generated energetic charges can promote the reactive oxygen species (ROS) generation through both chemical and energy transformation process, and release the heat through electron-phonon relaxation process, endowing the plasmonic nanostructures with the photodynamic and photothermal performance (Scheme S2, Supporting Information).

Furthermore, the electromagnetic field-mediated fluorescence enhancement and energetic carriers-induced photodynamic and photothermal performance can exhibit the similar ascending tendency. More importantly, the well-designed anisotropic architecture of nanosystems can further facilitate the charge carrier spatial separation based on the Fermi level alignment on disparate metals, leading to more remarkable hot electron generation and subsequently more effective photothermal and photodynamic performance.

In the present study, Pt dots were anisotropically grown at both ends of gold nanorods (Au NRs) to form Pt end-deposited Au nanorods (PEA NRs) with the LSPR maximum at 808 nm, which possess excellent plasmonic property, metal heterostructure, and anisotropic architecture. Upon 808 nm laser irradiation, an efficient electron-hole spatial separation along longitudinal axis of rods can occur in PEA NRs because of their end-deposition morphology, leading to more significant hot electron generation in PEA NRs compared with Pt body-deposited gold nanorods (PBA NRs) or traditional Au@Pt core–shell nanorods (PBA NRs) where the electron–hole separation is not efficient due to the homogeneous coating distribution over the whole body of Au NRs. X-ray shows the transmission electron microscopy (TEM) images of PEA, PBA, and Au NRs. Au NRs had homogeneous sizes with average lengths of 4.2 nm in length and 12.6 ± 2.1 nm in diameter. PBA NRs showed a more evident Pt deposition at the ends of Au NRs than that at the lateral sides, while PBA NRs showed a more even Pt distribution at the ends and sides of Au NRs.

This sophisticated nanosystem, CF-bPEA@siRNA NRs, was designed as a theranostic platform for NIR fluorescence imaging and phototherapy of cancer. As shown in Figure 1d, once intravenously administered to tumor-bearing mice, negatively charged CF-bPEA@siRNA NRs were expected to realize a long circulation time and high accumulation at the tumor region based on enhanced permeability and retention (EPR) effect. Biodistribution and tumor accumulation of CF-bPEA@siRNA NRs could be visualized through significantly amplified CF790 NIR fluorescence. The weak acidic microenvironment (pH 6.5) of tumor could initiate the charge reversal of CPP from negative to positive, beneficial for the cell uptake of CF-bPEA@siRNA NRs and following endosomal disruption. The released Nrf2 siRNA from CF-bPEA@siRNA NRs in acidic endosomal compartment (pH 4.5–5.5) could attenuate the cellular hyperthermia resistance and antioxidant performance, aiming to optimize the cellular microenvironment for PDT and PTT. Upon 808 nm laser irradiation, the combined PTT and PDT effects of CF-bPEA@siRNA NRs could significantly inhibit the tumor growth.

Au NRs were prepared through a seed-mediated method. With addition of 5-bromosalicylic acid that selectively blocks the side of Au NRs to inhibit Pt deposition, the platinum precursor (H2PtCl6) preferred to be deposited at the ends of Au NRs to form PEA NRs. Once Pt was nucleated on the rods, there was a thermodynamic preference for additional Pt growth on Pt rather than the exposed Au surface because of the higher cohesive and surface energies of Pt. To better elucidate the advantage of PEA NRs, PBA NRs with homogeneous Pt deposition on Au NRs were prepared in a similar process without addition of 5-bromosalicylic acid. Figure 2a and Figure S1a (Supporting Information) shows the transmission electron microscopy (TEM) images of PEA, PBA, and Au NRs. Au NRs had homogeneous sizes of 42.3 ± 4.2 nm in length and 12.6 ± 2.1 nm in diameter. PEA exhibited the island growth pattern (Volmer–Weber model) on PEA and PBA NRs, where PEA NRs showed Pt deposition at both ends of Au NRs while PBA NRs displayed the homogeneous Pt deposition over the whole body of Au NRs.

The elemental mapping (Figure 2b) confirmed that PEA NRs had more evident Pt deposition at the ends of Au NRs than that at the lateral sides, while PBA NRs showed a more even Pt distribution at the ends and sides of Au NRs. X-ray...
diffraction (XRD) patterns (Figure S1b, Supporting Information) further revealed the typical \{111\}, \{100\}, and \{110\} peaks of Pt existing in both PEA and PBA NRs, confirming the Pt deposition on Au NRs. Ultraviolet (UV)–visible (vis) near infrared spectra indicated Pt deposition on Au NRs could redshift the LSPR peak of Au NRs from 740 to 808 nm (Figure 2c and Figure S1c, Supporting Information).[19]

Furthermore, finite difference time domain (FDTD) simulation (Figure 2d) theoretically presented the spatial distribution of electric intensity in PEA and PBA NRs, where the more...
significant electric field enhancement occurred at the ends of PEA NRs compared with those of PBA NRs. Transient absorption (TA) spectroscopy measurements experimentally detected the generation and dynamics of energetic charge carries in PEA and PBA NRs,[20] corroborating the higher hot electron generation efficiency (Figure 2e) and slower charge decay speed (Figure S2, Supporting Information) of PEA NRs than PBA NRs, which is ascribed to the more effective electron–hole spatial separation efficiency of PEA NRs. Taken together, PEA NRs can produce strong electric field density and abundant hot electrons. The abundant hot electrons are beneficial for promoting the reactive oxygen species generation through both chemical and energy transformation process, and also for releasing the heat through electron-phonon relaxation process (Scheme S2, Supporting Information).

The significantly enhanced hot electron density of PEA NRs can promote photothermal and photodynamic performance. Photothermal performance of PEA, PBA, and Au NRs was

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Figure 2. Physicochemical characterization of PEA and PBA NRs. a) TEM images. b) Scanning transmission electron microscopy (STEM) images and energy dispersive X-ray spectroscopy (EDS) elemental mapping images. c) UV–vis NIR absorption spectra. d) Spatial distribution of enhanced electric field at LSPR excitation based on FDTD simulation. e) Transient absorption spectra of PEA and PBA NRs at representative delay time. f) Infrared thermal images of NR aqueous suspension (equivalent to 50 µg mL⁻¹ Au) irradiated by an 808 nm laser (0.75 W cm⁻²) for 600 s. g) ESR spectra of TEMP-¹O₂ spin adducts were generated by Au, PBA, and PEA NRs (equivalent to 25 µg mL⁻¹ Au) aqueous solution containing 0.3 mol L⁻¹ TEMP under 808 nm laser irradiation (0.75 W cm⁻², 10 min); h) NIR fluorescence emission spectra of free CF and various CF-PEA NRs with 1, 3.4, 5, and 10 kD of PEG linkers at excitation of 784 nm.
investigated by comparing their temperature elevation profiles under 808 nm laser irradiation (0.75 W cm\(^{-2}\), 10 min). Figure S3 (Supporting Information) shows PEA NRs could induce the most potent photothermal activity with a photothermal conversion efficiency of 55.4% (Figure S4a,b, Supporting Information), followed by PBA (52.9%) and Au NRs (49.3%), which could be clearly visualized by infrared thermal imaging (Figure 2f). The superior photothermal activity of PEA NRs compared with PBA NRs may be due to their higher hot electrons generation efficiency, which is beneficial for heat release through electron-phonon relaxation.

The photodynamic performance of PEA, PBA, and Au NRs was also investigated under 808 nm laser irradiation (0.75 W cm\(^{-2}\), 10 min) through electron spin resonance (ESR) spectroscopy, and 2,2,6,6-tetramethylpiperidine (TEMP, for \(^1\)O\(_2\)) as well as 5,5-dimethyl-1-pyrroline n-oxide (DMPO, for \(\cdot\)O\(_2\)\(-\)) and \(\cdot\)OH were exploited as ROS-sensitive trapping agent. Figure 2g and Figure S5a,b (Supporting Information) shows PEA NRs could induce the strongest ESR signals of \(^1\)O\(_2\), \(\cdot\)O\(_2\)\(-\), and \(\cdot\)OH, followed by PBA and Au NRs. Obviously, heterostructures (PEA and PBA NRs) can induce more efficient electron-hole separation than homostructures (Au NRs), and PEA NRs are more effective than PBA NRs, as a result of more ROS production. Moreover, both PEA and PBA NRs showed excellent photostability as demonstrated by Figure S6 (Supporting Information).

CF790, was attached to PEA NRs through PEG linker for enhancement of NIR fluorescence intensity. The LSPR absorption maximum (808 nm) of PEA NRs was very close to the fluorescence emission maximum (806 nm) of CF790, making it possible for the fluorescence amplification. To achieve the strongest NIR fluorescence, the distance between PEA NRs and CF790 was optimized by tuning the molecular weights of PEG linker (1, 3.4, 5, and 10 kDa), the length of which was estimated to be 4, 8, 10–20, and 25–30 nm, respectively.[21] The very short distance can result in fluorescence quenching, whereas the very long distance will have no enhancement in the fluorescence intensity.[60] The content of CF790 on various CF790-PEG conjugated PEA NRs (CF-PEA NRs) was controlled at the similar level (Figure S7a, Supporting Information),[22] and the hydrodynamic sizes of CF-PEA NRs became bigger and bigger with the increase of PEG molecular weight from 1k to 10k (Figure S7b, Supporting Information). Figure 2h shows that CF\(_{5k}\)-PEA NRs (CF790 was conjugated to PEA NRs through PEG linkers with the molecular weight of 1k) produced the reduced fluorescence intensity than free CF790 while CF\(_{3.4k}\)-PEA, CF\(_{5k}\)-PEA, and CF\(_{10k}\)-PEA NRs exhibited the enhanced intensity, where the enhancement of CF\(_{5k}\)-PEA NRs was the most remarkable. It means the appropriate PEG linker actually results in the largest NIR fluorescence amplification. Furthermore, the NIR fluorescence signal of CF\(_{5k}\)-PEA NRs could not be influenced by ROS (Figure S7c, Supporting Information), demonstrating the PDT process cannot affect the NIR fluorescence intensity.

The surface of CF\(_{5k}\)-PEA NRs was fabricated with thiol-modified PEG$_{3,4k}$-CPP to form CF$_{5k}$-b-PEA NRs with a hydrodynamic size of 222.4 ± 18.1 nm in culture medium for improving their biocompatibility, cellular uptake efficiency, and subsequent endosomal disruption. In vitro NIR fluorescence enhancement of CF\(_{5k}\)-b-PEA NRs was examined in MCF-7 cells. For comparison, other CF$_{1–10k}$-PEA NRs were similarly fabricated to form CF$_{1–10k}$-b-PEA NRs. After 6 h of incubation with various CF$_{1–10k}$-b-PEA NRs under weak acidic condition (pH 6.5), the cells showed similar dark-field signal intensities (Figure 3a), and Au element-based inductively coupled plasma-optical emission spectrometer (ICP-OES) analysis (Figure S8a, Supporting Information) further confirmed the similar Au contents in these cells. In comparison, the cellular uptake at neutral conditions (Figure S8a, Supporting Information) was lower than those at acidic conditions, demonstrating the potential cell penetration ability of pH-sensitive CPP under tumor acidic condition. However, NIR fluorescence microscopy (Figure 3b) revealed that the cells treated with CF$_{5k}$-b-PEA NRs showed weaker NIR fluorescence compared with those treated with free CF790, while the cells treated with CF$_{3.4k}$-b-PEA, CF$_{5k}$-b-PEA, and CF$_{10k}$-b-PEA NRs displayed the significantly enhanced NIR fluorescence, where CF$_{5k}$-b-PEA NRs could result in the most prominent cellular fluorescence enhancement, which was further confirmed by flow cytometry analysis (Figure S8b, Supporting Information). This trend is in accordance with the profile of fluorescence emission spectra of various CF-PEA NRs (Figure 2h), corroborating CF$_{5k}$-b-PEA NRs can exhibit the highest cellular NIR fluorescence intensity.

The phototherapeutic effect of CF$_{5k}$-b-PEA NRs was assessed by 3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl))-2H-tetrazolium (MTS) assay under 808 nm laser irradiation. For comparison, PEA and Au NRs were also similarly fabricated with CPP and CF790 to form CF$_{5k}$-b-PBA and CF$_{5k}$-b-Au NRs. After 6 h of treatment with various concentrations of these NRs in acidic culture medium (pH 6.5) followed by another 18 h of incubation in normal culture medium, the viability of MCF-7 cells was found to be less affected (Figure S9a, Supporting Information), demonstrating the excellent biocompatibility of these NRs. However, when cells were treated with these NRs for 6 h in acidic culture medium followed by 5 min of 808 nm laser irradiation (0.5 W cm\(^{-2}\)) and another 18 h of incubation in normal culture medium, both CF$_{5k}$-b-PEA and CF$_{5k}$-b-PBA NRs could more remarkably reduce the cell viability than CF$_{5k}$-b-Au NRs (Figure 3c), where CF$_{5k}$-b-PEA NRs could cause more severe reduction than CF$_{5k}$-b-PBA NRs based on their more significant photothermal and photodynamic performance. Furthermore, calcein acetoxymethyl (AM)/propidium iodide Live/dead cell staining assay (Figure 3d) was carried out to further corroborate the biocompatibility and phototherapeutic effect of CF$_{5k}$-b-PEA NRs in MCF-7 cells. In comparison, all these NRs displayed lower phototherapeutic effects under neural condition (Figure S9b, Supporting Information), supporting pH-sensitive CPP can improve the phototherapeutic efficiency of these NRs under acidic condition, which is potentially ascribed to their enhanced cellular uptake.

The effective PDT effect of CF$_{5k}$-b-PEA NRs was ascribed to their large amount ROS production. However, since aerobic ROS can stimulate nuclear factor NF-E2 related factor 2 (Nrf2) cellular signaling pathway to produce phase II enzymes responsible for antioxidant defense, the current NIR light-activated oxidative injury induced by CF$_{5k}$-b-PEA NRs probably has been dramatically attenuated.[11a,23] Moreover, the PTT effect of CF$_{5k}$-b-PEA NRs can also enhance HSP70 expression, leading to cellular hyperthermia resistance. Thus, attenuating the cellular antioxidant defense and hyperthermia resistance
potentially can potentiate the PDT and PTT effect. A thiol-modified i-motif DNA/Nrf2 siRNA chimera was immobilized on the surface of CF5k-bPEA NRs to form CF5k-bPEA@siRNA NRs (Figure S10, Supporting Information) for strengthening both PDT and PTT effect. As analyzed by agarose gel electrophoresis (Figure 4a), CF5k-bPEA@siRNA NRs could exhibit a pH-responsive siRNA release behavior, suggesting that i-motif DNA segment of CF5k-bPEA@siRNA NRs can undergo the allosteric effect at a low pH environment, facilitating the Nrf2 siRNA chimera release. CF5k-bPEA@siRNA NRs could also be effectively internalized into MCF-7 cells (Figure S10c, Supporting Information). Confocal fluorescence microscopy further revealed that FITC-labeled siRNA could colocalize with Lyso-Tracker Red stained endosomes when cells were incubated with CF5k-bPEA@FITC-siRNA NRs (without CPP terminal) for 6 h, but could diffuse into the cytosol when cells incubated with CF5k-bPEA@FITC-siRNA NRs (with CPP terminal) (Figure 4b). This result confirms CF5k-bPEA@siRNA NRs can efficiently release siRNA into cytosol due to CPP modification. Western blot analysis (Figure 4c) indicated that the Nrf2, HO-1 (a typical phase II enzyme), and HSP 70 expression in cells treated with CF5k-bPEA@siRNA NRs was much lower than those of cells treated with CF5k-bPEA NRs, and furthermore, these Nrf2 expressions were inversely proportional to the increased concentration (12.5, 25, and 50 \( \mu \)g mL\(^{-1}\)) of CF5k-bPEA@siRNA NRs (Figure S11a, Supporting Information), and the Nrf 2 gene knockdown efficiency were 11.48%, 41.18%, and 66.27%, respectively (Figure S11b, Supporting Information), meaning Nrf2 siRNA has successfully taken effect.

The downregulation of Nrf2 potentially can attenuate antioxidant defense and hyperthermia resistance capability, making cells more susceptible to ROS and heat injury as well as leading to enhanced NIR-triggered phototherapeutic effect of CF5k-bPEA NRs compared with CF5k-bPEA NRs. Under 808 nm laser irradiation, CF5k-bPEA@siRNA NRs were found to cause more severe cell death than CF5k-bPEA NRs, as shown by MTS assay (Figure 4d). Further hierarchical oxidative stress response measurements corroborated that upon 808 nm laser irradiation CF5k-bPEA@siRNA NRs could trigger higher cellular ROS level (Figure 4e) and IL-6 cytokine release (Figure 4f), and cause more significant mitochondrial membrane depolarization (Figure 4g) and superoxide generation.

Figure 3. In vitro NIR fluorescence amplification and NIR laser activated phototherapeutic effect of CF5k-bPEA NRs in MCF7 cells. a) Dark field images and b) NIR fluorescence images of MCF7 cells treated with free CF or various CF1–10k-bPEA NRs (equivalent to 25 \( \mu \)g mL\(^{-1}\) Au) for 6 h. c) MTS viability assessment of MCF-7 cells treated with different concentrations of CF5k-bAu, CF5k-bPBA, and CF5k-bPEA NRs (according to Au content) for 24 h under 5 min of 808 nm laser irradiation (0.5 W cm\(^{-2}\)). d) Live/dead cell staining of MCF-7 cells treated with CF5k-bAu, CF5k-bPBA, and CF5k-bPEA NRs (equivalent to 25 \( \mu \)g mL\(^{-1}\) Au) for 24 h with or without 5 min of 808 nm laser irradiation (0.5 W cm\(^{-2}\)). * \( P < 0.05 \), ** \( P < 0.01 \).
(Figure 4g) than CF₅k-bPEA NRs. Annexin-V-FITC/PI-based apoptosis analysis by flow cytometry also supported that CF₅k-bPEA@siRNA NRs induced 10.3% of early apoptotic cells and 32.2% of late apoptotic cells while CF₅k-bPEA NRs only did 7.7% and 24.6%, respectively (Figure 4h). However, without NIR laser irradiation, all these hierarchical oxidative stress responses induced by both NRs kept the similar levels, comparable to those of untreated cells (Figure S12a–d, Supporting Information). All above results demonstrate that incorporation of DNA/Nrf2 siRNA chimera into CF₅k-bPEA NRs can further strengthen their NIR-triggered cell injury.

Encouraged by the in vitro NIR fluorescence behaviors of various CF-bPEA NRs and prominent phototherapeutic effect of CF₅k-bPEA@siRNA NRs, their in vivo fluorescence imaging and tumor growth inhibition performance were further verified in MCF-7 tumor-bearing mice. After intravenously administered with various CF-bPEA@siRNA NRs, NIR fluorescence image of MCF-7 tumor-bearing mice captured at 24 h post-administration (Figure 5a) showed that free CF790 and CF 1k-bPEA@siRNA NRs did not exhibit noticeable NIR fluorescence in the whole body of mice, but CF₃.₄k-bPEA@siRNA, CF₅k-bPEA@siRNA, and CF₁₀k-bPEA@siRNA NRs exhibited stronger fluorescence
signals than free CF790. The significant tumor accumulation was clearly displayed by these NRs, where CF5k-bPEA@siRNA NRs still showed the strongest fluorescence signal. Au element-based ICP-OES analysis for the tumor and major organs (Figure S13, Supporting Information) indicated that various CF-bPEA@siRNA NRs had similar accumulation and circulation behaviors in mice, meaning the most promising in vivo NIR fluorescence image exhibited by CF5k-bPEA@siRNA NRs should originate from their highest fluorescence amplification ability rather than tumor accumulation ability. Both Au and Pt elements had similar biodistribution, as demonstrated by various Au/Pt mass ratios of CF-bPEA@siRNA, which are very close to their theoretical Au/Pt values of 11.60 (Table S2, Supporting Information), suggesting their excellent in vivo stability. Moreover, the photoacoustic images (Figure 5b) of tumor region further revealed the tumor accumulation behavior of CF5k-bPEA@siRNA NRs at various time periods after the administration, demonstrating the even distribution of CF5k-bPEA@siRNA NRs in tumor tissue. In vivo photothermal effect of CF5k-bPEA@siRNA NRs was evaluated through infrared thermal imaging. After intravenously administered with PBS, CF5k-bPEA NRs, CF5k-bPEA@siRNA NRs, the tumor region of mice were subjected to 808 nm laser irradiation (0.75 W cm\(^{-2}\), 10 min) at 24 h post-administration. Both CF5k-bPEA and CF5k-bPEA@siRNA NRs could rapidly increase the tumor temperature from \(\approx 30\) to \(\approx 45\) °C within 10 min, potentially causing the similar level of cell damage (Figure 5c and Figure S14, Supporting Information).

In vivo phototherapeutic effect of CF5k-bPEA@siRNA NRs was further evaluated through monitoring the tumor growth rates of MCF-7 tumor-bearing mice. Mice were intravenously administered with PBS, siRNA, CF5k-bPEA NRs, or CF5k-bPEA@siRNA NRs under 808 nm laser irradiation or not. The tumor volume was measured and plotted as a function of time (Figure 5d and Figure S15a, Supporting Information).
It was found that without NIR laser irradiation the tumors of mice administered with these materials could rapidly grow within 15 days, and there was no evident difference in the tumor growth rates (Figure S15a,b, Supporting Information). However, under 808 nm laser irradiation, administration with CF5k-bPEA or CF5k-bPEA@siRNA NRs could dramatically regress the tumor growth, where CF5k-bPEA@siRNA NRs even completely eradicated the tumors at the end of treatment, showing more remarkable tumor regression than CF5k-bPEA NRs (Figure 5d,e). In comparison, administration of PBS or siRNA only could weakly inhibit the tumor growth of mice. To further corroborate the therapeutic effects, the tumor tissues were dissected at the end of treatment for evaluation of the pathological changes through hematoxylin and eosin (H&E) histology analysis (Figure 5f). Without 808 nm laser irradiation, little damage was found in the tumor tissues of mice treated by these materials (Figure S15c, Supporting Information). However, under 808 nm laser irradiation, the tumor tissues of CF5k-bPEA or CF5k-bPEA@siRNA NRs treated mice were severely damaged, where CF5k-bPEA@siRNA NRs were more effective than CF5k-bPEA NRs. All these pathological results of tumor tissues are consistent with the tumor growth inhibition results, supporting CF5k-bPEA@siRNA NRs possess more prominent phototherapeutic effect than CF5k-bPEA NRs, which is ascribed to their attenuated antioxidant defense and hyperthermia resistance. Above results demonstrate again the combined therapeutic effect of CF5k-bPEA@siRNA NRs based on PTT, PDT, and gene therapy.

Since the biocompatibility of the nanomaterials plays an important role for their future applications, a series of physiology parameters of mice, such as the body weight fluctuations, H&E staining of main organs, and the serum biochemistry parameters, were carefully monitored after the treatment. It could be observed that there was no noticeable difference in the body weight fluctuations of mice between treatment group and control group (Figure S16, Supporting Information). Histology analysis of major organs from mice indicated there was no appreciable abnormality or noticeable organ damage in heart, liver, spleen, lung, and kidney (Figure S17, Supporting Information). The parameters of serum biochemistry assays were also in normal range (Table S1, Supporting Information). All these in vivo biodistribution, therapeutic effects, and biocompatibility studies prove that CF5k-bPEA@siRNA NRs hold great promise for cancer therapy.

In summary, PEA NRs could produce more potent PTT and PDT performance than PBA NRs under 808 nm laser irradiation. The NIR fluorescence intensity of CF790 could be more remarkably amplified by PEA NRs when CF790 was attached to PEA NRs through 5k PEG. Biocompatible CF5k-bPEA NRs could be efficiently internalized into MCF-7 cells, presenting the promising cellular NIR fluorescence and inducing severe cell damage under 808 nm laser irradiation. Further CF5k-bPEA@siRNA NRs were prepared to knockdown Nrf2 gene in cells, capable of attenuating the cellular antioxidant defense and hyperthermia resistance capability, and inducing more significant PDT and PTT effect than CF5k-bPEA NRs. After intravenous administration to MCF-7 tumor-bearing mice, CF5k-bPEA@siRNA NRs still exhibited the most promising NIR fluorescence imaging performance and more significant tumor growth inhibition than CF5k-bPEA NRs. Thus, CF5k-bPEA@siRNA NRs hold great potential as a theranostic nanosystem for cancer diagnosis and therapy.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

Keywords
anisotropic heterostructures, fluorescence amplification, hot electrons, phototherapy, theranostics

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