Supporting Information

$NaCeF_4$:Gd,Tb Scintillator as an X-ray Responsive Photosensitizer for Multimodal Imaging-Guided Synchronous Radio/Radiodynamic Therapy

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Experimental Section

Materials

Cerium(III) acetate hydrate ($Ce(CH_3CO_2)_3 \cdot xH_2O$, 99.9%), Gadolinium(III) acetate hydrate ($Gd(CH_3CO_2)_3 \cdot xH_2O$, 99.9%), Terbium(III) acetate hydrate ($Tb(CH_3CO_2)_3 \cdot xH_2O$, 99.9%), Lanthanum(III) acetate hydrate ($La(CH_3CO_2)_3 \cdot xH_2O$, 99.9%), 2',7'-dichlorofluorescin diacetate (DCFH-DA), 3,3',5,5'-tetramethylbenzidine (TMB), 1,3-diphenylisobenzofuran (DPBF), Nitro blue tetrazolium (NBT) and Salicylic acid (SA) were purchased from Sigma-Aldrich. Ammonium fluoride (NH_4F, 98%) was purchased from Alfa Aesar. Oleic acid (OA) and 1-octadecene (ODE) were obtained from Aladdin. CCK-8 kit, 4', 6-diamidino-2-phenylindole (DAPI), 5,5-dimethyl-1-pyrroline-N-oxide (DMPO), and 5-tert-butoxycarbonyl-5-methyl-1-pyrroline-N-oxide (BMPO) were purchased from Dojindo Laboratories. γ-H2AX antibody was purchased from Abcam company. Bax polyclonal antibody and Bcl-2 polyclonal antibody were purchased from Bioworld Technology. Cy3 labelled antibody was purchased from Beyotime Biotechnology (Nanjing, China). F-12K Medium, 1640 medium, fetal bovine serum (FBS), and Penicillin-Streptomycin Solution were acquired from Gibco (Shanghai, China). Others were obtained from Sinopharm Chemical Reagent Co., Ltd. Deionized water was supplied by a recirculating deionized water system (Millipore, Direct Q5, 18.2 MΩ·cm at 25 °C). A549 human lung carcinoma cell line and CT26 mouse colon carcinoma cell line were purchased from Cell Bank of Chinese Academy of Sciences (Shanghai, China). Male BALB/c mice or nude mice were obtained from Nanjing Peng Sheng Biological Technology Co, Ltd (Nanjing, China).

Synthesis of rod-like $NaCeF_4$:Gd,Tb scintillating nanoparticles (ScNPs)

The rod-like $NaCeF_4$:Gd,Tb ScNPs were prepared via a modified high temperature reaction method.[1] In a typical synthesis route, $Ce(CH_3CO_2)_3 \cdot xH_2O$ (1.2 mmoL), $Gd(CH_3CO_2)_3 \cdot xH_2O$ (0.4

mmoL), and $Tb(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) were loaded in a 100 mL three-necked flask containing 14 mL of OA and 16 mL of ODE. After degassing for 10 min. The mixture was heated to 120 °C and stirred for 30 min, then cooled down below 50 °C. Then a methanol solution containing NH_4F (8 mmoL) and NaOH (5 mmoL) was injected rapidly. The resulting mixture was stirred and heated to above 100 °C to remove the residual methanol from the reaction system. Upon the complete removal of methanol, the solution was rapidly heated to 320 °C and maintained this temperature for 1.5 h under nitrogen. The resulting products were precipitated with centrifugation by adding ethanol, washed with ethanol, and finally dispersed in 5 mL of chloroform.

Synthesis of control nanoparticles

For the synthesis of $NaLaF_4$:Gd,Tb, $La(CH_3CO_2)_3 \cdot xH_2O$ (1.2 mmoL), $Gd(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) and $Tb(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) were loaded in a 100 mL three-necked flask containing 14 mL of OA and 16 mL of ODE. The following synthetic procedure was as the same as that of $NaCeF_4$:Gd,Tb.

For the synthesis of $NaCeF_4$:Gd,La, $Ce(CH_3CO_2)_3 \cdot xH_2O$ (1.2 mmoL), $Gd(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) and $La(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) were loaded in a 100 mL three-necked flask containing 14 mL of OA and 16 mL of ODE. The following synthetic procedure was as the same as that of $NaCeF_4$:Gd,Tb.

For the synthesis of $NaLaF_4$:Gd, $La(CH_3CO_2)_3 \cdot xH_2O$ (1.6 mmoL) and $Gd(CH_3CO_2)_3 \cdot xH_2O$ (0.4 mmoL) were loaded in a 100 mL three-necked flask containing 14 mL of OA and 16 mL of ODE. The following synthetic procedure was as the same as that of $NaCeF_4$:Gd,Tb.

Surface modification of ScNPs

Polyethylene glycol (PEG) grafted poly (maleic anhydride-alt-1-octadecene) (C_{18}PMH-PEG) was synthesized according to our previously reported procedure.[2] Amphipathic and biocompatible

C_{18}PMH-PEG was used to functionalize $NaCeF_4$:Gd,Tb scintillators to afford them hydrophilic property via hydrophobic interaction. In brief, 5 mL of C_{18}PMH-PEG solution (chloroform, 20 mg mL^{-1}) were added into 1 mL of $NaCeF_4$:Gd,Tb solution (chloroform, 10 mg mL^{-1}). After sonicated for 30 min, the solution was kept stirring at room temperature overnight. Finally, the solution was dried with nitrogen and then DI water was added to obtain ScNP-PEG aqueous solution. The PEGylation of control nanoparticles followed the method above.

Characterization

Transmission electron microscope (TEM, FEI-TECNAI-G20, America) was used to obtain morphology of samples. Elemental species was analyzed by energy dispersive spectra (EDS). The phase and crystallography of the products were conducted with X-ray diffractometer with Cu Kα radiation (λ=1.54056 Å) with a Lynxeye one-dimensional detector (XRD, Bruker, D8 advance, Germany). X-ray photoelectron spectroscopy (XPS, Thermo, ESCALAB 250XI, America) was used to analyze the valence state of Ce. UV/vis-NIR spectrophotometer (UV-3600, Shimadzu, Japan) was used to measure light absorption spectrum. Dynamic light scattering (DLS, Malvern, Zetasizer Nano ZS90, UK) was used to measure the hydrodynamic size and zeta potential. Fluorescence spectra and lifetimes were measured by fluorescence spectrometer (Edinburgh Instruments, FLS980, UK). The concentrations of lanthanide elements were determined by inductively coupled plasma mass spectrometry (ICP-MS, Thermo, ELEMENT 2, America). The ROS generation was confirmed by electron spin resonance (ESR, JEOL RESONANCE, JES-X320, Japan) spectra.

UV and X-ray excited emission spectra and luminescence

The UV excited excitation spectrum and emission spectrum of ScNP-PEG were recorded by fluorescence spectrometer (Edinburgh Instruments, FLS980, UK). The X-ray excited emission

spectrum of ScNP powders was recorded through a spectrometer embedded with a laboratory X-ray source (Bruker D8 advance with Cu Kα radiation) and the fluorescence was taken with digital camera.

Superoxide anion (·O_2^-) scavenging assay

In this assay, ·O_2^- was generated using the NADH/PMS reaction system. NBT as the trapping agent of ·O_2^- can be converted to blue chromagen formazan with a characteristic absorption at 560 nm.[3] Specifically, NADH (1 mM), NBT (0.25 mM), ScNP-PEG (0, 250, 500, 1000 and 2000 μg mL^{-1}), and PMS (15 μM) were prepared. Then, a 1.75 mL of mixture containing H_2O (700 μL), NADH (350 μL), NBT (350 μL), and ScNP-PEG (350 μL) was prepared. After that, the reaction was initiated by 350 μL of PMS. The absorbance at 560 nm of each solution was monitored with UV-Vis spectroscopy for 20 min.

Hydroxyl radical (·OH) scavenging assay

In this assay, ·OH was generated using the $FeSO_4/H_2O_2$ reaction system. SA as the trapping agent of ·OH can be converted to 2'3'-dihydroxy-benzoic acid (DHB) with a characteristic absorption at 510 nm.[4] Specifically, $FeSO_4$ (4 mM) was prepared with HAc-NaAc buffer (pH 4.0). H_2O_2 (40 mM) and ScNP-PEG (0, 200, 400, 800 and 1600 μg mL^{-1}) were prepared with deionized water. Then, 2.2 mL of mixture containing SA (550 μL), H_2O_2 (550 μL), ScNP-PEG (550 μL) and $FeSO_4$ (550 μL) was prepared. The mixture was placed in the dark for 10 min. The absorbance peak at 510 nm of the solution was monitored with UV/vis spectroscopy.

X-ray induced extracellular ROS generation

Extracellular superoxide anion (·O_2^-) generation was examined by photo-degradation (410 nm) of DPBF. Each tube containing 50 μg mL^{-1} of DPBF and 25 μg mL^{-1} of ScNP-PEG or control

nanoparticles was irradiated with X-ray (160 kV, 40 mA) of 0, 2, 4, 6, 8, 10, 15, and 20 Gy, respectively, and immediately scanned with UV/vis-NIR spectrophotometer (Shimadzu, UV-3600). Extracellular hydroxyl radical (·OH) was detected by TMB as the trapping agent with the characteristic absorption peak at 652 nm. Each tube containing 200 μg mL^{-1} of TMB and 100 μg mL^{-1} of ScNP-PEG or control nanoparticles was irradiated with X-ray (160 kV, 40 mA) of 0, 2, 4, 6, 8, 10, 15, and 20 Gy, respectively, and immediately scanned with UV/vis-NIR spectrophotometer (Shimadzu, UV-3600). The generations of both $\cdot O_2^-$ and ·OH were also confirmed by the standard method of ESR with BMPO and DMPO as the trapping agent, respectively. Each tube containing 25 mM of BMPO and 25 μg mL^{-1} of ScNP-PEG or control nanoparticles was irradiated with X-ray of 0, 2, 4, 6, 8, 10, 15, and 20 Gy, respectively, and immediately measured by ESR. Each tube containing 25 mM of DMPO and 100 μg mL^{-1} of ScNP-PEG or control nanoparticles was irradiated with X-ray of 0, 2, 4, 6, 8, 10, 15, and 20 Gy, respectively, and immediately measured by ESR.

UV light induced extracellular ROS generation

In this assay, for $\cdot O_2^-$ measurement, 400 μg mL^{-1} of ScNP-PEG was mixed with 50 μM of NBT in advance. Thereafter, the mixture was irradiated with UV light at 250 nm for up to 20 min. The absorbance at 560 nm of each solution was monitored with UV/vis spectroscopy. For ·OH measurement, 400 μg mL^{-1} of ScNP-PEG was mixed with 1.5 mM of SA in advance. Thereafter, the mixture was irradiated with UV light at 250 nm for up to 20 min. The absorbance peak at 510 nm of the solution was monitored with UV/vis spectroscopy.

In vitro cytotoxicity

In vitro cytotoxicity assay was conducted with CCK-8 kit to determine the relative cell viabilities. A549 cells were first seeded into 96-well plates at a density of 8×10^3 cells overnight. Until adherence, cells were incubated with different concentrations of ScNP-PEG for 24 h. To further evaluate the X-ray (160 kV, 40 mA) induced cell damage, A549 cells were seeded in 96-wells plates at the density of 2×10^3 cells overnight. Cells were treated with 50 μg mL^{-1} ScNP-PEG and irradiated by X-ray (160 keV, RS-2000 Pro Biological Irradiator) with a series of radiation doses (0, 2, 4, and 6 Gy). Upon irradiation finished, cell medium was replaced with fresh medium. Cells were cultured for another 3 days followed by measuring the relative cell viabilities by CCK-8 assay.

The endocytosis of ScNP-PEG

Hydrophobic Rose Bengal (RB) was used to trace the endocytosis of ScNP-PEG. For the labeling, 1 mL of ScNP-PEG solution (1 mg mL^{-1}) was mixed with 1 mg of hydrophobic RB in DI water. The mixture was stirred for 6 h in the dark. Unbound excess dye was then removed by centrifugation and the pellets were washed with DI water for several times. The obtained RB labeled ScNP-PEG were re-suspended in PBS and stored at 4 °C. A549 cells were incubated with 50 μg mL^{-1} of ScNP-PEG for different time (0, 1, 6, 10, and 24h). After that, cells were washed with PBS and fixed in 4% paraformaldehyde, followed by staining cell nuclei with DAPI. Cells were imaged using confocal microscopy (OLYMPUS, FV1200, Japan).

γ-H2AX immunofluorescence analysis

A549 cells were seeded in 6-well plates at the density of 2×10^5 cells overnight. At the beginning, cells were incubated with 50 μg mL^{-1} of ScNP-PEG for 6 h followed by irradiation with X-ray (160 kV, 40 mA) at a dose of 6 Gy (160 keV, RS-2000 Pro Biological Irradiator). Upon finished,

cells were incubated for another 30 min and then fixed in 4% paraformaldehyde. After that, cells were permeabilized with 0.2% Triton X-100. Next, cells were blocked with 1% bovine serum albumin (BSA) for 1 h and further incubated with anti-phospho-histone γ-H2AX mouse monoclonal antibody overnight. Afterwards, the cells were further incubated with Cy3-conjugated sheep anti-mouse secondary antibody for 1 h. The coverslips were washed out with PBS followed by staining cell nuclei with DAPI. Cells were imaged using confocal microscopy (OLYMPUS, FV1200, Japan).

Clonogenic assay

A549 cells were seeded in 6-well plates with different amount (125, 250, 500, 1000) per well. Cells were treated with PBS and 50 μg mL^{-1} of ScNP-PEG, respectively. Thereafter, the cells were irradiated by X-ray (160 kV, 40 mA) with a series of radiation doses (0, 2, 4, and 6 Gy). After that, cells were washed with PBS and fresh medium was replaced every three days for 10 days. The colonies were fixed by 4% paraformaldehyde and then stained with Giemsa dye. Only colonies containing at least 50 cells were counted to calculate the colony formation rate using the standard linear quadratic model. Each treatment was performed in triplicate.

Intracellular ROS generation

A549 cells were seeded into 35 mm confocal dishes at the density of 2×10^5 cells. Cells were divided into six groups including: 1) PBS, 2) $NaLaF_4$:Gd,Tb-PEG, 3) $NaCeF_4$:Gd,Tb-PEG, 4) X-ray (6 Gy), 5) $NaLaF_4$:Gd,Tb-PEG + X-ray (6 Gy), and 6) $NaCeF_4$:Gd,Tb-PEG + X-ray (6 Gy). In group 2) and 5), cells were incubated with 50 μg mL^{-1} of $NaLaF_4$:Gd,Tb-PEG for 6 h. In group 3) and 6), cells were incubated with 50 μg mL^{-1} of $NaCeF_4$:Gd,Tb-PEG for 6 h. Cells in group 4), 5), and 6) were irradiated with X-ray (160 kV, 40 mA) at 6 Gy and then incubated for 1 h. Thereafter

the cells were washed with PBS and incubated with 10 μM of DCFH-DA suspended in serum-free medium for 20 min. When all the treatments finished, cells were stained with DAPI. Finally, the cells were imaged using confocal microscopy (OLYMPUS, FV1200, Japan) to obtain the fluorescence images.

Western blot analysis

B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein (Bax) were evaluated by western blot analysis. Cells were treated with PBS and 50 μg mL^{-1} of ScNP-PEG, respectively. Twenty-four hours later, the cells were irradiated with X-ray (160 kV, 40 mA) of 6 Gy. At 48 h post-X-ray irradiation, cells in different groups were collected and lysed. Protein concentrations were calculated using BCA protein assay kit. Equal quantities of proteins were loaded and separated by SDS-PAGE. Then the proteins were transferred onto polyvinylidene difluoride membranes in a Tris-glycine transfer buffer, followed by blocking with 5% skim milk at room temperature for 2 h. The membrane was incubated with primary antibodies (anti-Bax, and anti-Bcl-2) at 4˚C overnight. The membranes were washed and incubated with secondary HRP-conjugated antibody (anti-rabbit IgG) at 25˚C for 2 h. Membranes were washed and imaged with Gel Logic system (2200 Pro, Crestream, USA).

Blood circulation and biodistribution

All animals were acclimated to the animal facility at least one week prior to experimental procedures. Healthy male BALB/c nude mice were intravenously injected with 10 mg kg^{-1} of ScNP-PEG. Blood were collected near 50 μL at various time points post intravenous injection, followed by weighted and added to a conical flask containing 10 mL of hot aqua regia. The content of Ce, Gd and Tb were measured by ICP-MS (Thermo, ELEMENT 2, America). In order to test

the tumor uptake of ScNP-PEG, 1×10^7 of A549 cells suspended in 50 μL of PBS were inoculated at the right back of male BALB/c nude mice to develop lung tumor model. Mice bearing A549 tumor were intravenously injected with the same dose of ScNP-PEG and sacrificed at 24 h. Tumors and major organs including liver, spleen, kidney, heart and lung were dissociated, weighed, digested and then measured by ICP-MS.

In vitro and in vivo imaging

For *in vitro* X-ray excited fluorescence (XEF) imaging, ScNP-PEG solutions with different concentrations (0-25 mg mL^{-1}) were scanned under a multi-modal *in vivo* imaging system (Bruker In Vivo FX Pro) equipped with a detecting CCD (ML4002, Finger Lakes Instrumentation, USA). The solutions were irradiated with various excitation powers (25 kV-45 kV) by fixing the exposure time at 2 min and exposure times (1-4 min) by fixing the excitation power at 45 kV. For *in vivo* XEF imaging, male BALB/c nude mice were intra-tumor injected with ScNP-PEG (25 mg mL^{-1}, 0.05 mL) and scanned under the same instrument.

For *in vitro* T_1/T_2 MR imaging, $NaCeF_4$:Gd,Tb, $NaLaF_4$:Gd,Tb, and $NaLaF_4$:Gd solutions with various concentrations of Gd ions (0-1 mM) were scanned under a 3-T clinical MR scanner (GE Healthcare, USA). For *in vivo* T_1/T_2 MR imaging, A549-bearing male BALB/c nude mice were intra-tumor injected with ScNP-PEG (4 mg mL^{-1}, 0.05 mL) and then scanned with the same equipment.

For *in vitro* CT imaging, ScNP-PEG solutions with different concentrations (0-50 mM) were scanned under a CT imaging instrument (GE discovery CT750 HD, Healthcare, America). For *in vivo* CT imaging, A549 tumor-bearing male BALB/c nude mice were intra-tumor injected with ScNP-PEG (10 mg mL^{-1}, 0.05 mL) and scanned under the same instrument.

In vivo combination therapy

Male BALB/c nude mice were first fed with standard laboratory chow diet for one week. To develop lung tumor model, 1×10^7 of A549 cells suspended in 50 μL of PBS were inoculated at the right back of mice. When the tumor volumes reached to 70 mm^3, the mice were divided into four groups including: 1) PBS, 2) ScNP-PEG, 3) X-ray (6 Gy) and 4) ScNP-PEG + X-ray (6 Gy). Firstly, the tumor-bearing mice of groups 2) and 4) were intravenously injected with 200 μL of ScNP-PEG (12 mg kg^{-1}). Twenty-four hours later, the tumor-bearing mice of groups 3) and 4) were irradiated with X-ray (160 kV, 40 mA) at 6 Gy. Tumor growth and body weight of each mouse were recorded every two days within 30 days. The length (a) and width (b) of the tumors were measured by a digital vernier caliper with tumor size calculated as the following formula: $V = 1/2ab^2$, where V (mm^3) is the volume of the tumor. When the whole experiment finished, all the mice were sacrificed under protocols approved by the laboratory animal center of Soochow University. The tumors were dissected and weighed to evaluate the therapeutic efficacy of different groups. Meanwhile, to develop colon tumor model, 1×10^6 of CT26 cells suspended in 50 μL of PBS were also inoculated at the right back of male BALB/c mice. When the tumor sizes reached about 50 mm^3, the mice were randomly divided and treated like the way of treating A549 tumors as mentioned above.

Tumor biopsies staining

For ROS staining, tumors were embedded in tissue freezing medium at -20 ^oC. After completely frozen, the tumor slices were fixed in acetone and washed with PBS. Then the tumor slices were incubated with DCFH-DA (20 μM) for 1 h followed by staining with DAPI for 10 min. The slices

were imaged by confocal laser scanning microscope (CLSM, Zeiss Axio-Imager LSM-800, Germany).

For H&E staining, tumors were fixed in 10% formaldehyde solution and embedded in paraffin. Then the paraffin slices were staining with hematoxylin and eosin (H&E) and imaged under fluorescence microscope (Olympus, IX73, Japan).

For TUNEL staining, tumors were fixed in 10% formaldehyde solution and embedded in paraffin. Then the paraffin slices were stained with TdT-mediated dUTP Nick-End Labeling kit (TUNEL) and imaged under confocal laser scanning microscope (CLSM, Zeiss Axio-Imager LSM-800, Germany).

For Bax and Bcl-2 staining, tumors were fixed in 10% formaldehyde solution and embedded in paraffin. Then the paraffin slices were stained with anti-Bax and anti-Bcl-2 polyclonal antibodies, respectively. Then the biopsies were stained with secondary HRP-conjugated antibody (anti-rabbit IgG) and then imaged under fluorescence microscope (Olympus, IX73, Japan).

In vivo safety evaluation

Healthy male BALB/c nude mice with or without intravenously injecting 25 mg kg^{-1} of ScNP-PEG were sacrificed at 21 d. Blood samples were obtained for hematology and biochemistry analysis. All the analysis items were finished at Shanghai Model Organisms Center, Inc. As for the blood biochemistry index, we measured the hepatic function markers of alanine transferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and total protein (TP); renal function markers of blood urea nitrogen (BUN). Meanwhile, major organs such as heart, liver, spleen, lung, kidney, stomach, and intestine were stained with hematoxylin and eosin (H&E), and examined under a digital microscope (Olympus, IX73, Japan).

Statistical analysis

The experimental data were quantitatively expressed as Mean ± SEM, and analyzed by SPSS software (version 20.0; IBM Corp., Armonk, NY, USA) using independent t-test or one-way analysis of variance (ANOVA). A statistical significance of $P < 0.05$ was selected, with (*) for $p < 0.05$, (**) for $p < 0.01$, and (***) for $p < 0.001$ respectively.

References

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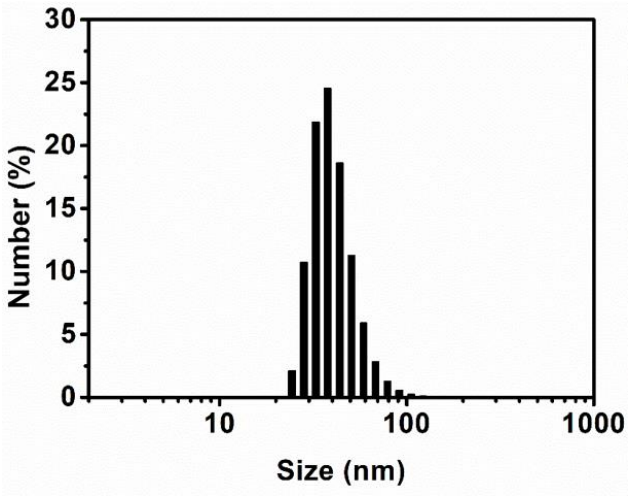

Figure S1. Hydrodynamic size of ScNP-PEG in DI water measured by DLS measurement.

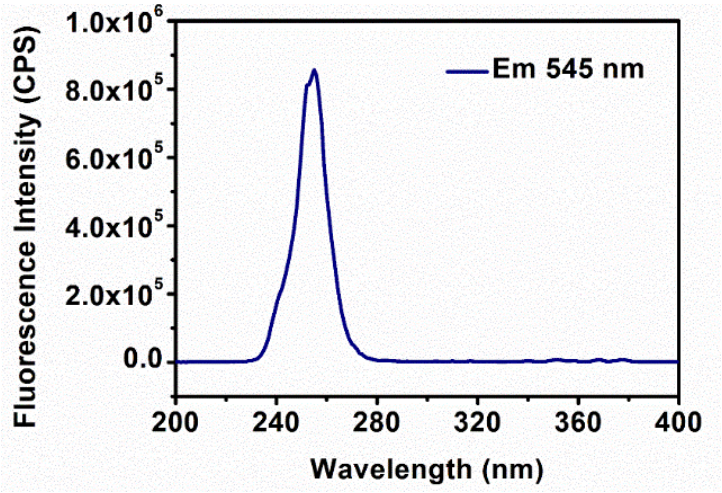

Figure S2. Excitation spectrum of ScNP-PEG monitored at the emission of 545 nm.

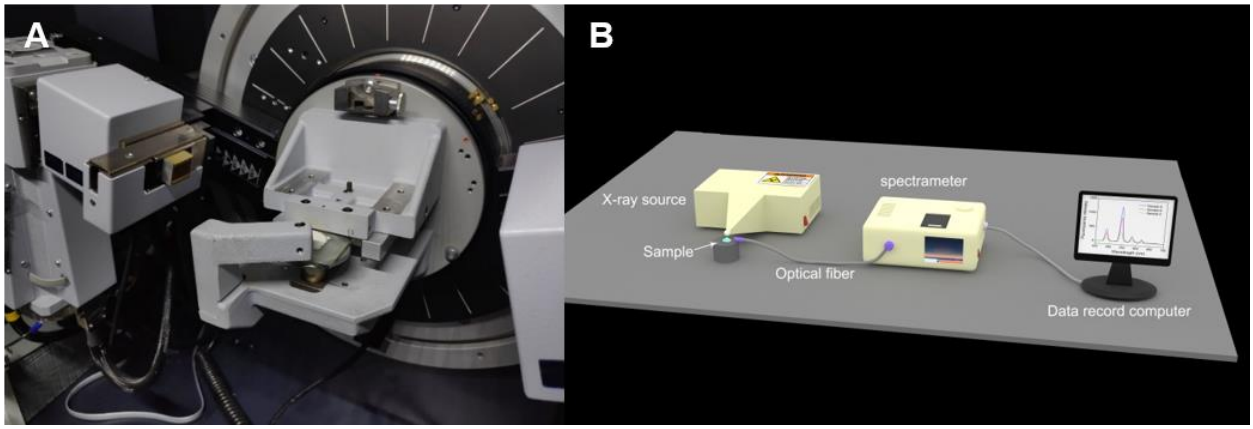

Figure S3. Experimental setup for X-ray excited fluorescence (XEF) spectrum measurement. (A) Lynxeye one-dimensional detector (Bruker, D8 advance) was used for providing X-ray source. (B) The XEF spectrum of scintillator was recorded through a spectrometer (NOVA) embedded within a laboratory X-ray source (Bruker D8 advance with Cu Kα radiation).

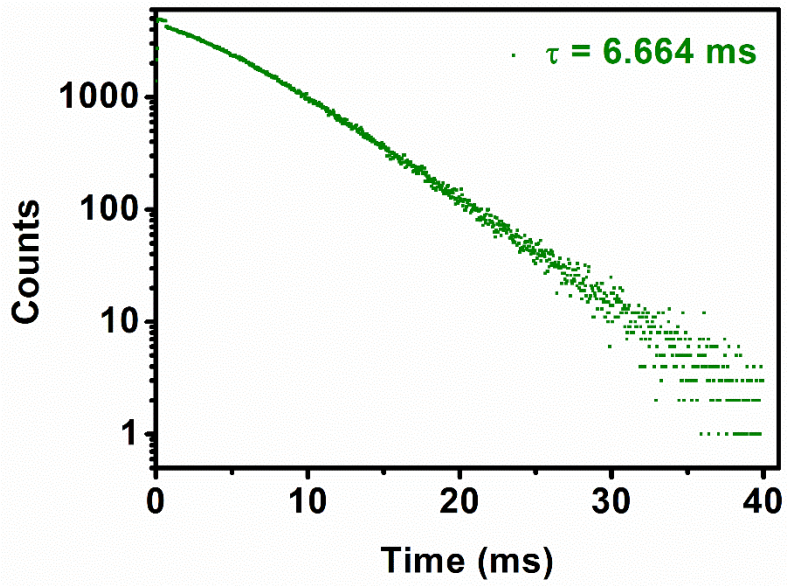

Figure S4. Luminescence decay curve of ScNP-PEG.

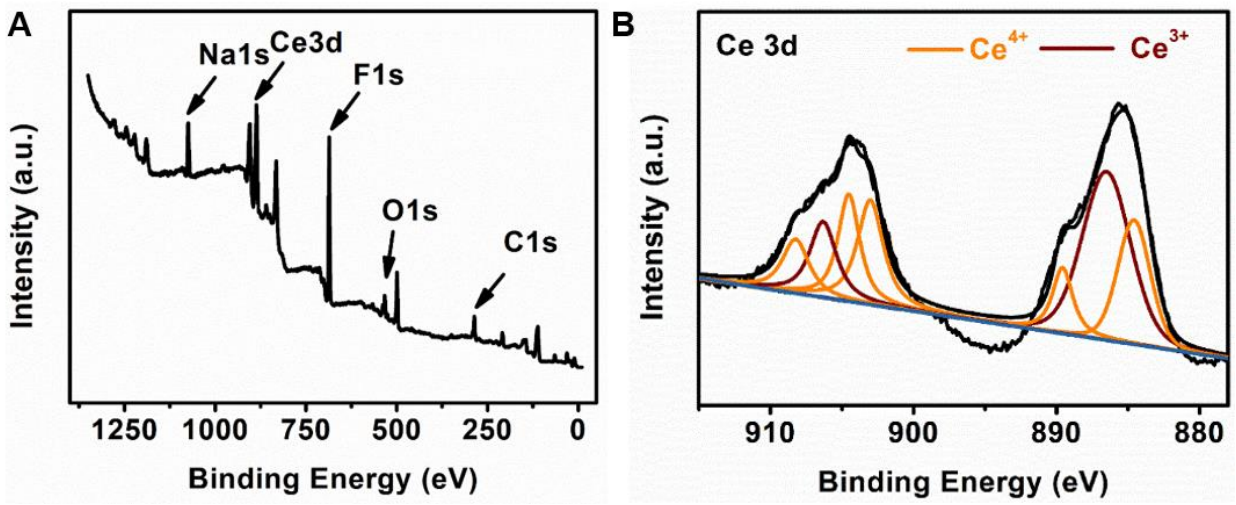

Figure S5. X-ray photoelectron spectroscopy (XPS) analysis of chemical valences of Ce ions. (A) XPS survey spectrum of ScNP. (B) XPS spectrum of Ce ions.

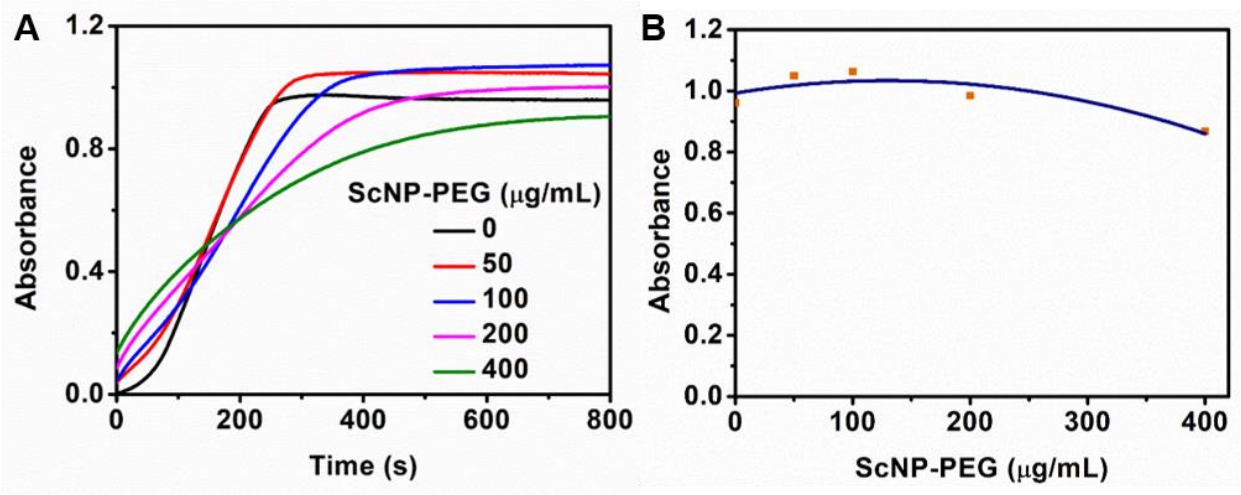

Figure S6. The superoxide anion ($\cdot O_2^-$) scavenging activity of ScNP-PEG with NBT as the probe. (A) The UV/vis absorbance of NBT. (B) The absorbance tendency of NBT at 560 nm.

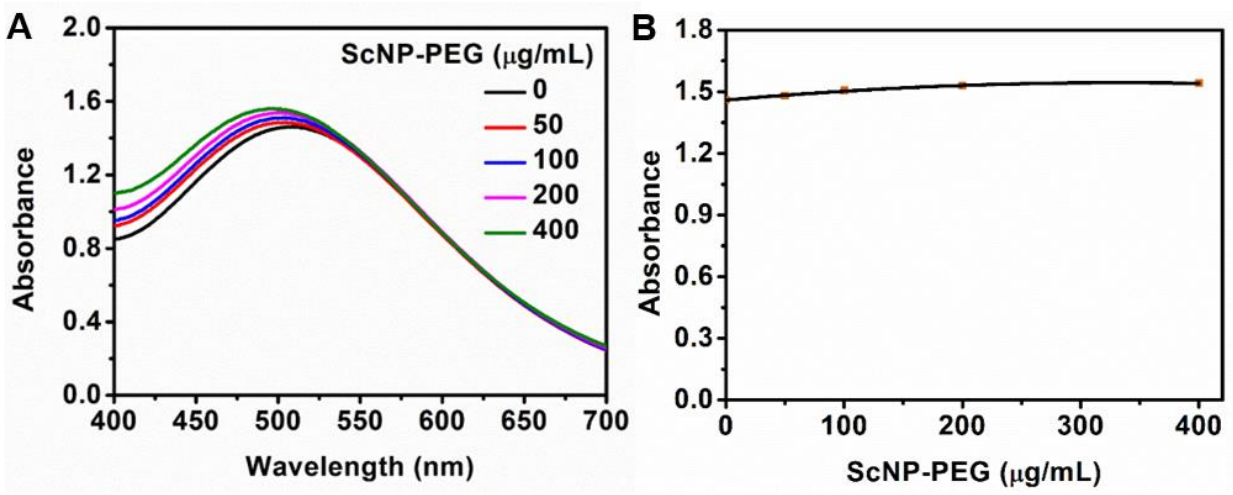

Figure S7. The hydroxyl radical (·OH) scavenging activity of ScNP-PEG with SA as the probe. (A) The UV/vis absorbance of SA. (B) The absorbance tendency of SA at 510 nm.

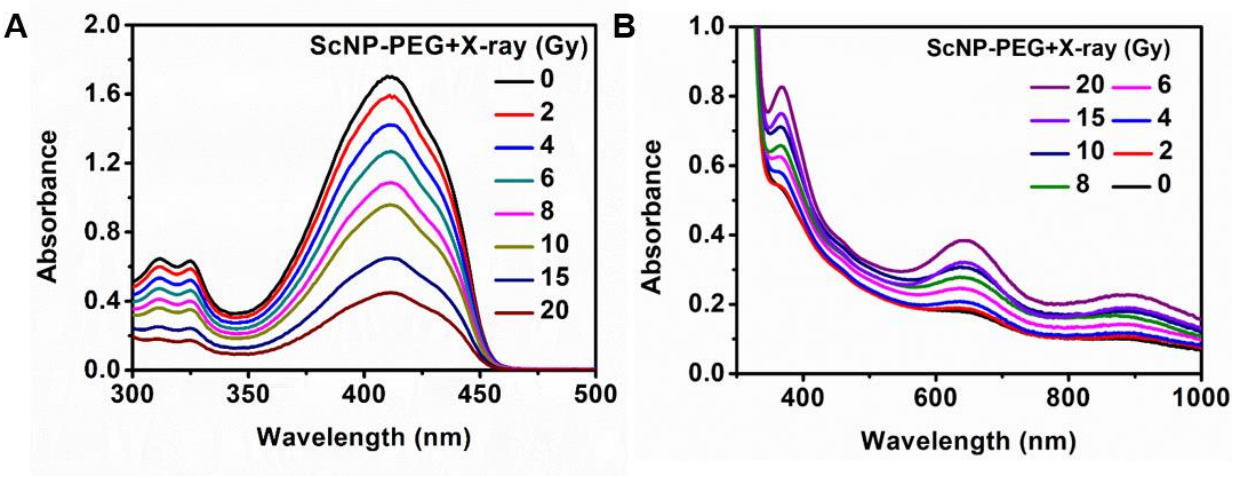

Figure S8. The UV/vis absorbance of ROS probes. (A) The superoxide anion ($\cdot O_2^-$) generation of ScNP-PEG under X-ray irradiation with DPBF as the probe. (B) The hydroxyl radical (·OH) generation of ScNP-PEG under X-ray irradiation with TMB as the probe.

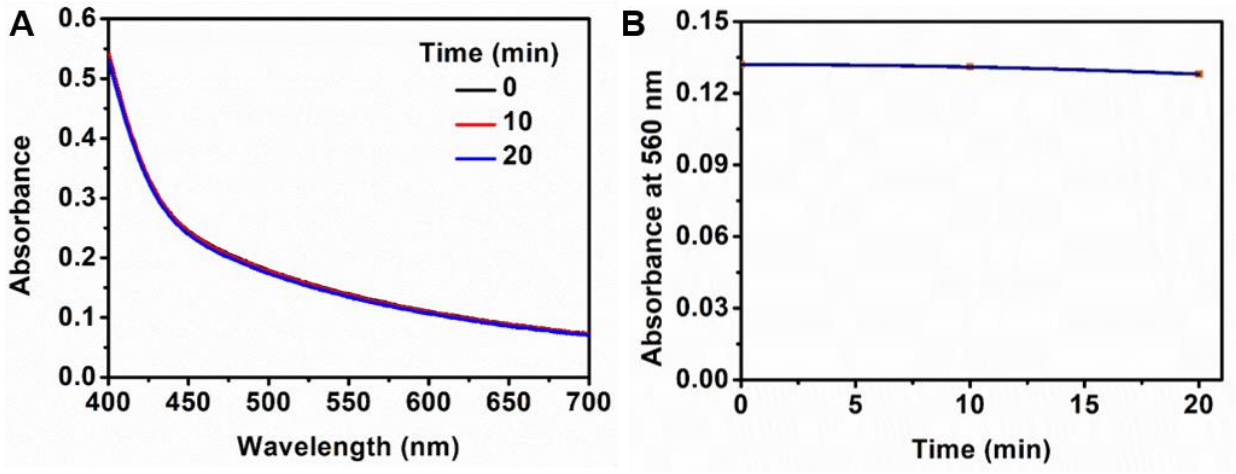

Figure S9. The superoxide anion ($\cdot O_2^-$) generating activity of ScNP-PEG under UV light irradiation at 250 nm with NBT as the probe. (A) The UV/vis absorbance of NBT. (B) The absorbance tendency of NBT at 560 nm.

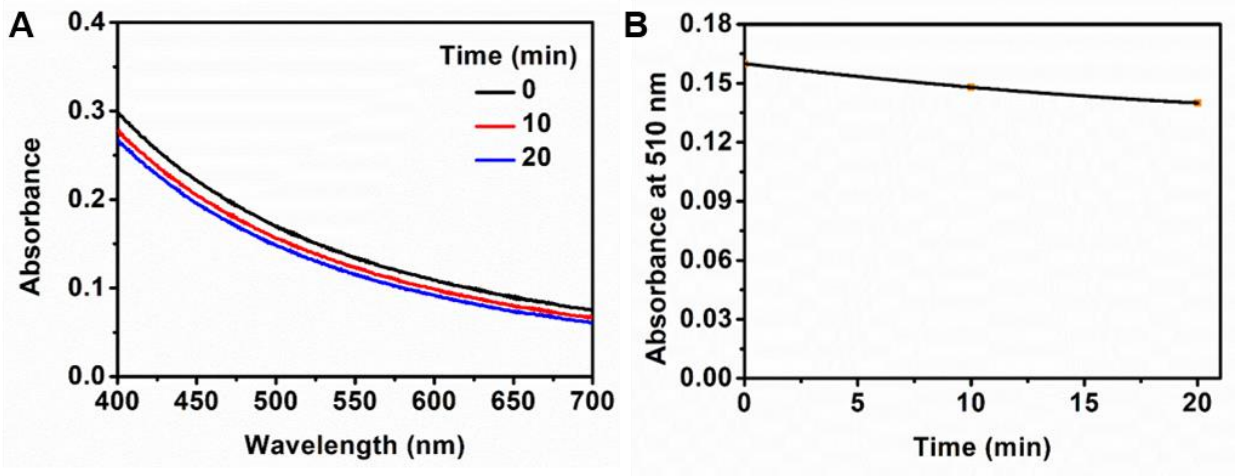

Figure S10. The hydroxyl radical ($\cdot OH$) generating activity of ScNP-PEG under UV light irradiation at 250 nm with SA as the probe. (A) The UV/vis absorbance of SA. (B) The absorbance tendency of SA at 510 nm.

Table S1. The efficiency (η) of ScNP-PEG induced RDT at different X-ray irradiation doses (D).

D (Gy)	*bm - bc*	*qm - qc*	*η*
2	27.59	13.32	8.80
4	40.64	26.05	7.25
6	57.12	32.67	6.48
8	60.05	43.09	5.64
10	107.58	47.63	6.65
15	140.33	56.32	5.60
20	186.28	60.45	5.23

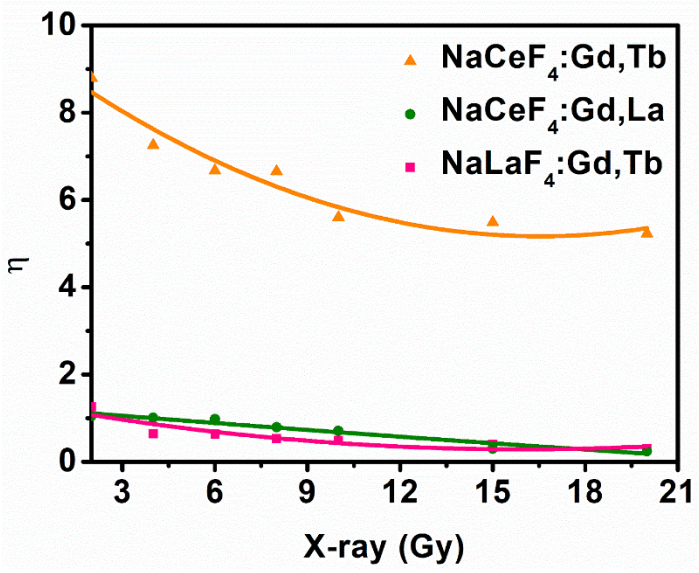

Figure S11. The comparison of efficiency (η) of different nanoparticles induced RDT at different X-ray irradiation doses (D).

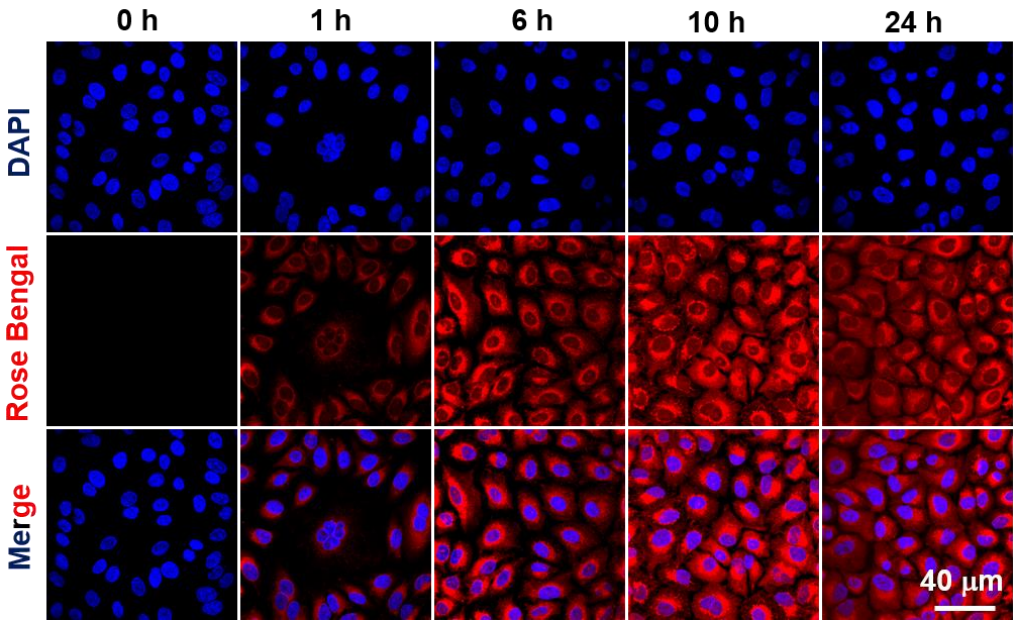

Figure S12. The endocytosis of ScNP-PEG labeled with Rose Bengal imaged by laser scanning confocal microscope.

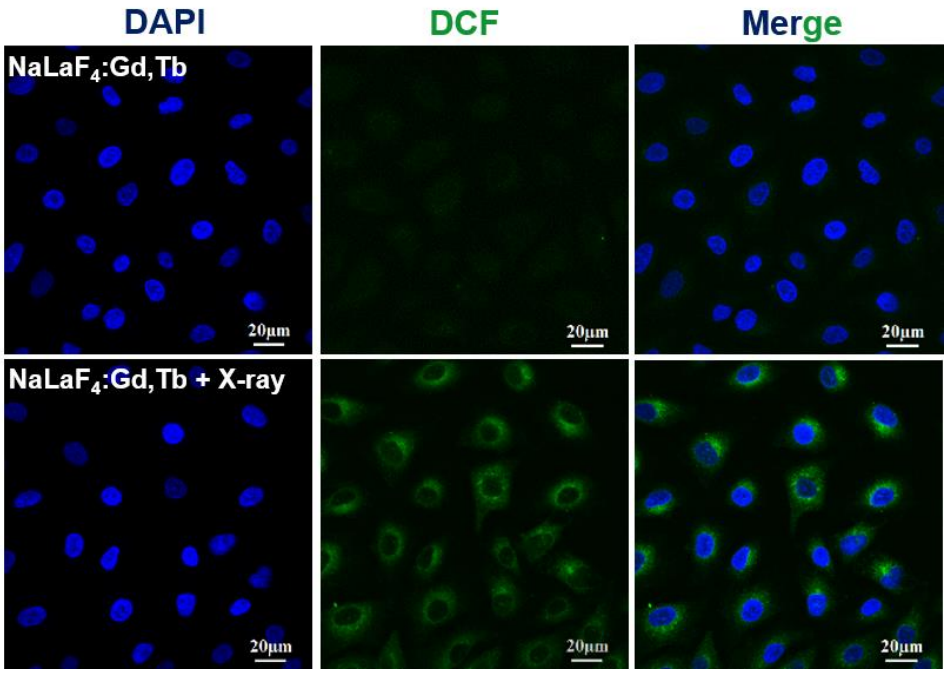

Figure S13. The fluorescence imaging of cell oxidative stress. A549 cells were stained with DCFH-DA for ROS detection.

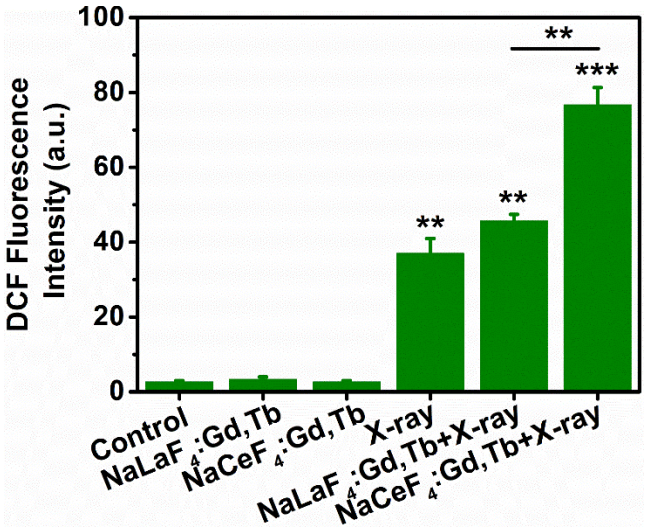

Figure S14. Quantification of the degree of cell oxidative stress. A549 cells were stained with DCFH-DA for ROS detection. (*p < 0.05, **p < 0.01, ***p < 0.001).

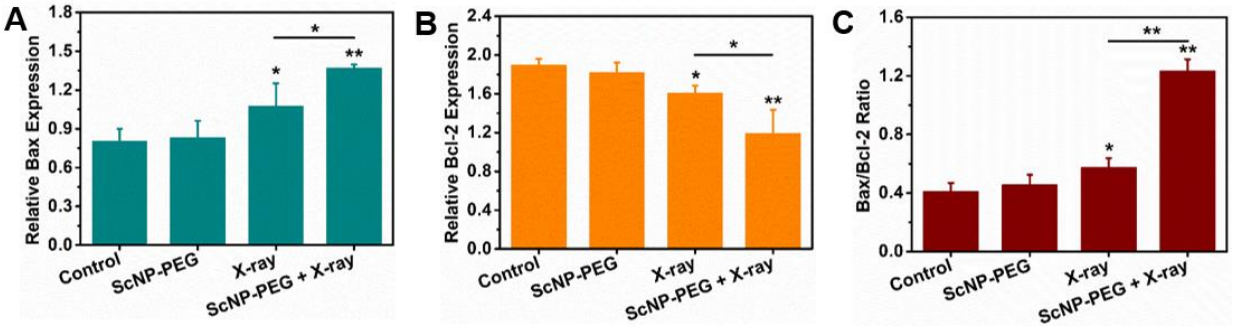

Figure S15. (A) The quantification of expression levels of ROS-related proteins. (A) The quantification of expression levels of Bax assessed by western blot. (B) The quantification of expression levels of Bcl-2 assessed by western blot. (C) The quantification of Bax/Bcl-2 ratios. (*p < 0.05, **p < 0.01, ***p < 0.001).

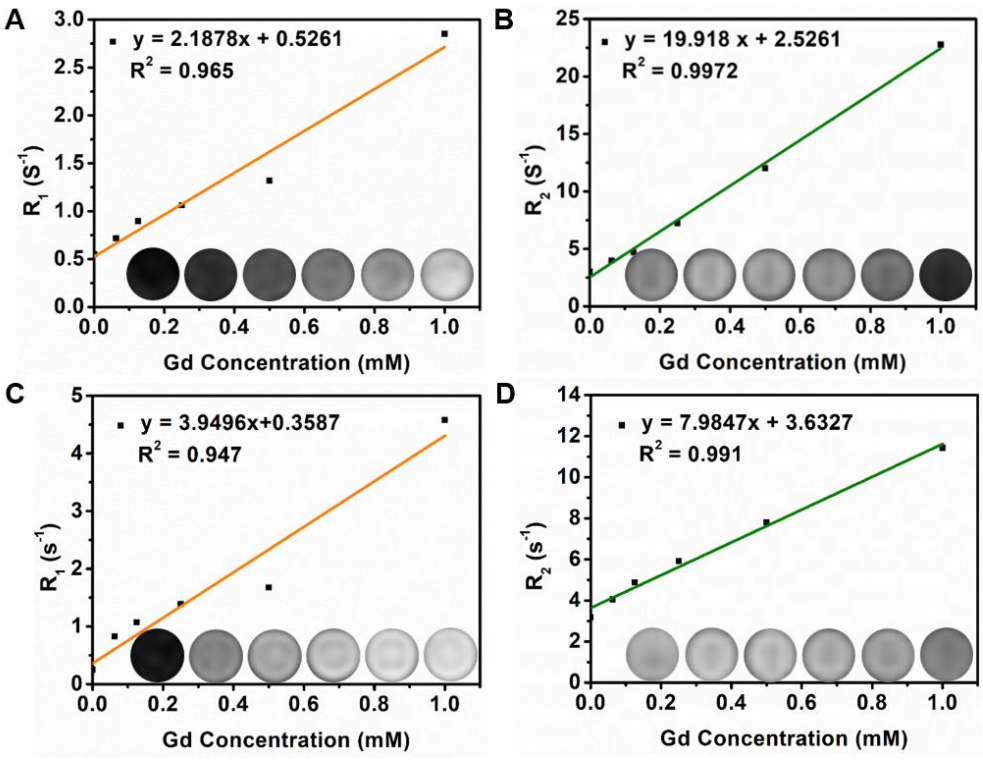

Figure S16. *In vitro* T_1/T_2-MR imaging of different concentrations of control nanoparticles. (A, B) *In vitro* T_1/T_2-MR imaging of different concentrations of $NaLaF_4$:Gd,Tb-PEG. The r_2/r_1 ratio was calculated to be 9.1. (C, D) *In vitro* T_1/T_2-MR imaging of different concentrations of $NaLaF_4$:Gd-PEG. The r_2/r_1 ratio was calculated to be 2.0.

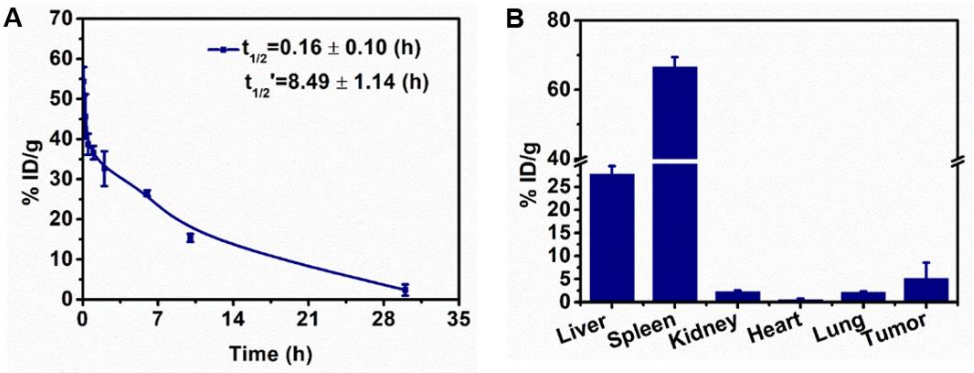

Figure S17. (A) The blood circulation of ScNP-PEG measured by ICP-MS. (B) The biodistribution of ScNP-PEG measured by ICP-MS at 24 h post-injection.

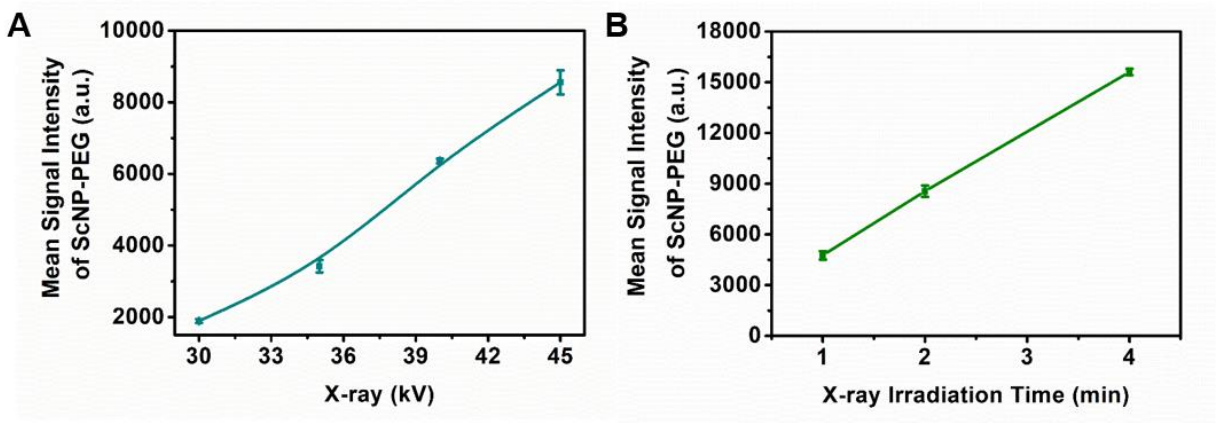

Figure S18. The quantification of fluorescence intensities at tumor site. (A) The mean fluorescence intensity of tumor sight under X-ray irradiation with different irradiation voltage. (B) The mean fluorescence intensity of tumor sight under X-ray irradiation with different irradiation time.

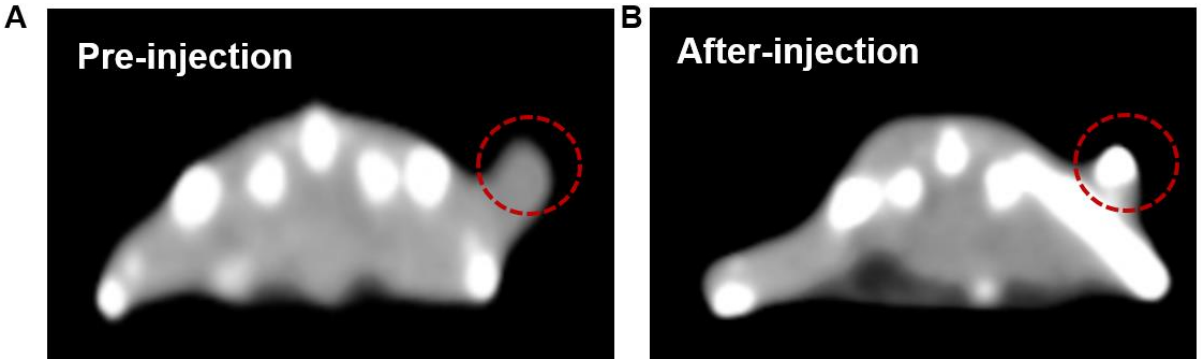

Figure S19. *In vivo* CT imaging by intra-tumor injecting 25 mg kg^{-1} of ScNP-PEG in A549 tumor-bearing nude mice. (A) CT imaging of tumor before injection. (B) CT imaging of tumor after i.t. injection.

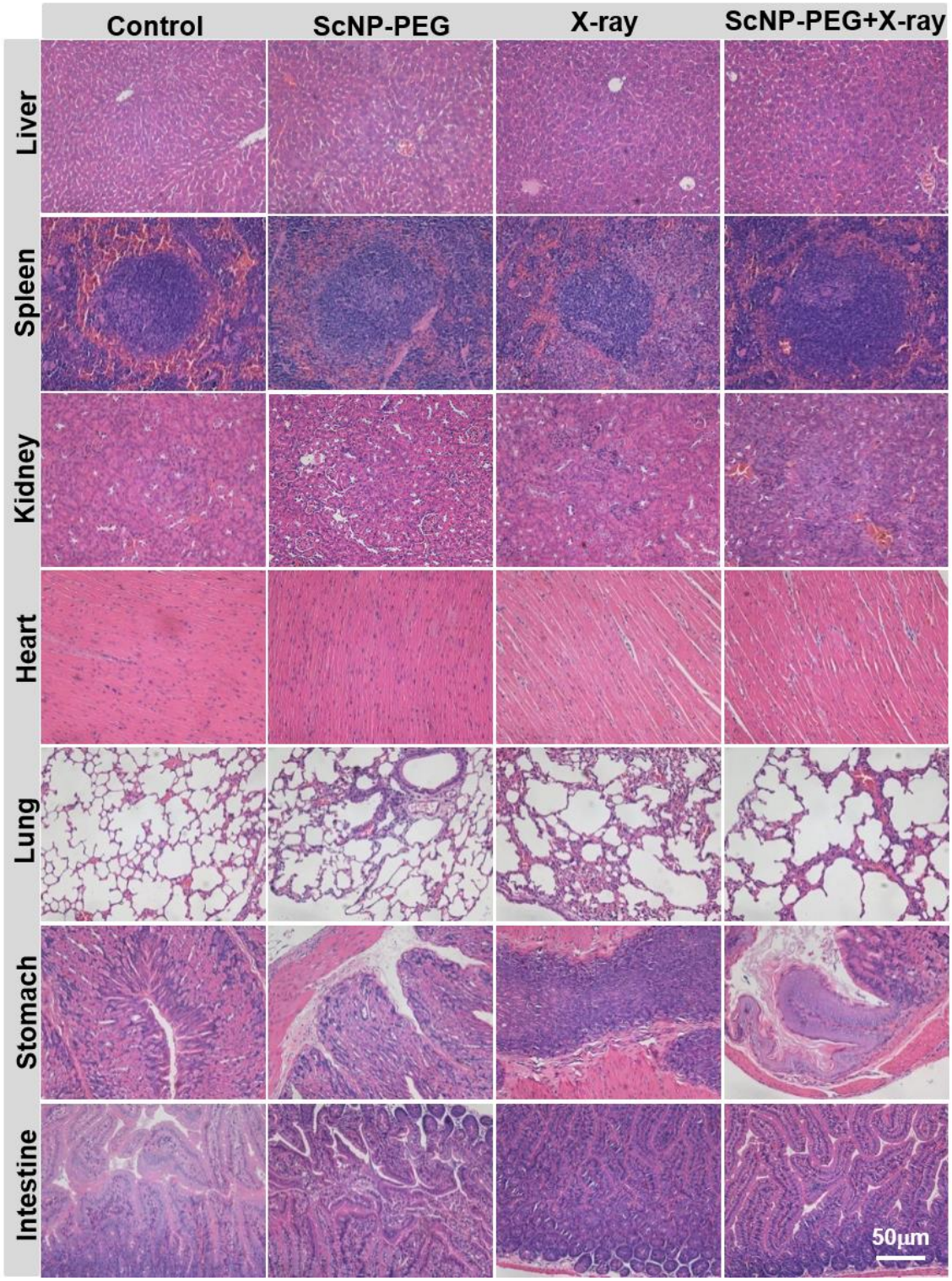

Figure S20. *In vivo* toxicity assessments of living organs affected with ScNP-PEG as well as X-ray irradiation. The living organs were collected at the 30th day.

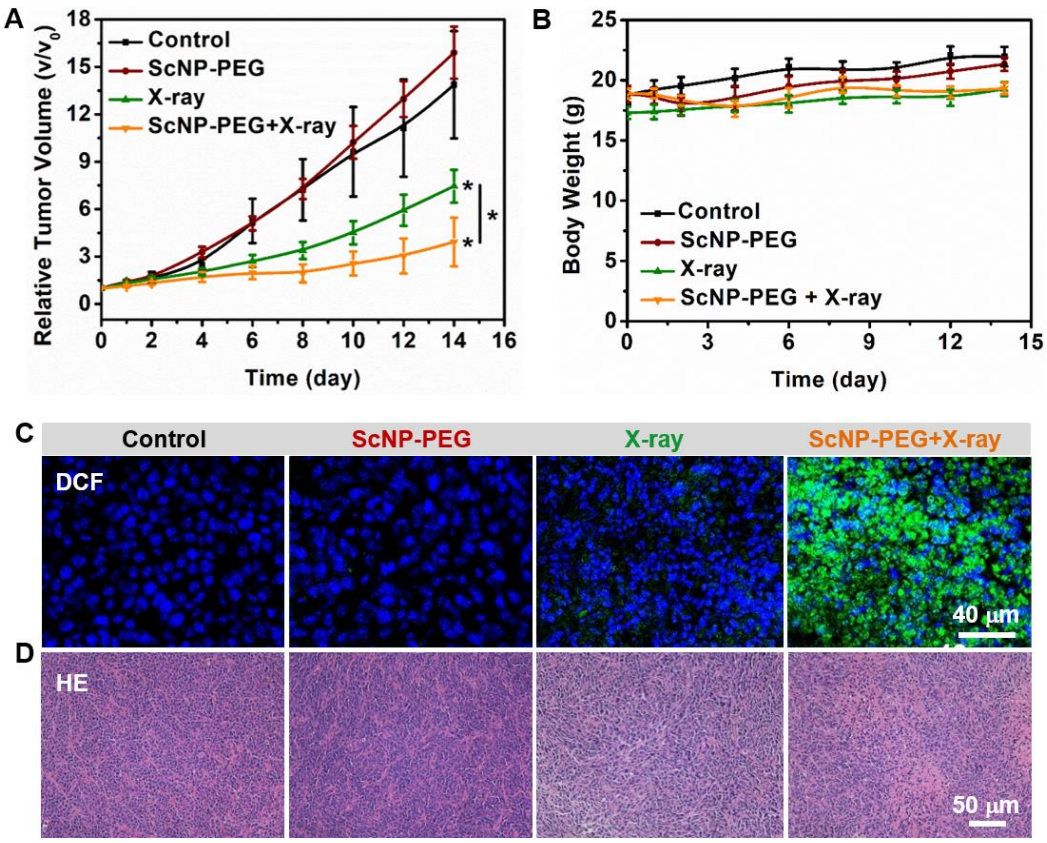

Figure S21. *In vivo* combined RT and RDT of CT26 tumors. (A) Tumor growth curves of mice in various treatments groups: 1) PBS, 2) ScNP-PEG alone, 3) X-ray (6 Gy) alone, and 4) ScNP-PEG+X-ray (6 Gy). (B) The changes of body weights in different groups. (C) Images of DCFH-DA stained tumor slices from different groups of mice. (D) Images of H&E stained tumor slices from different groups of mice. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

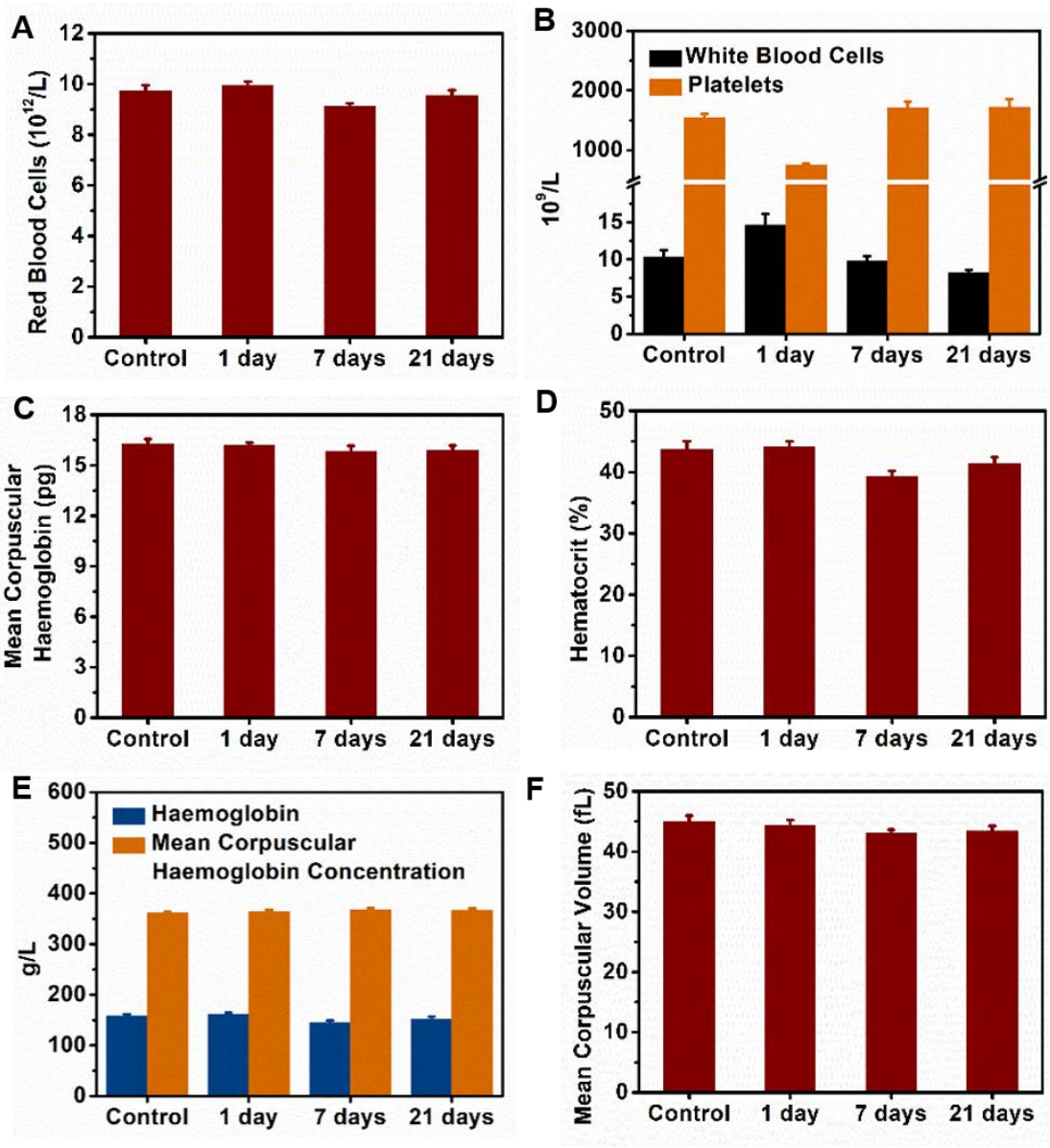

Figure S22. *In vivo* long-term toxicity assessments of ScNP-PEG. (A-F) Blood routine examination at 0, 1, 7, and 21 days after *i.v.* injecting 25 mg kg^{-1} of ScNP-PEG.

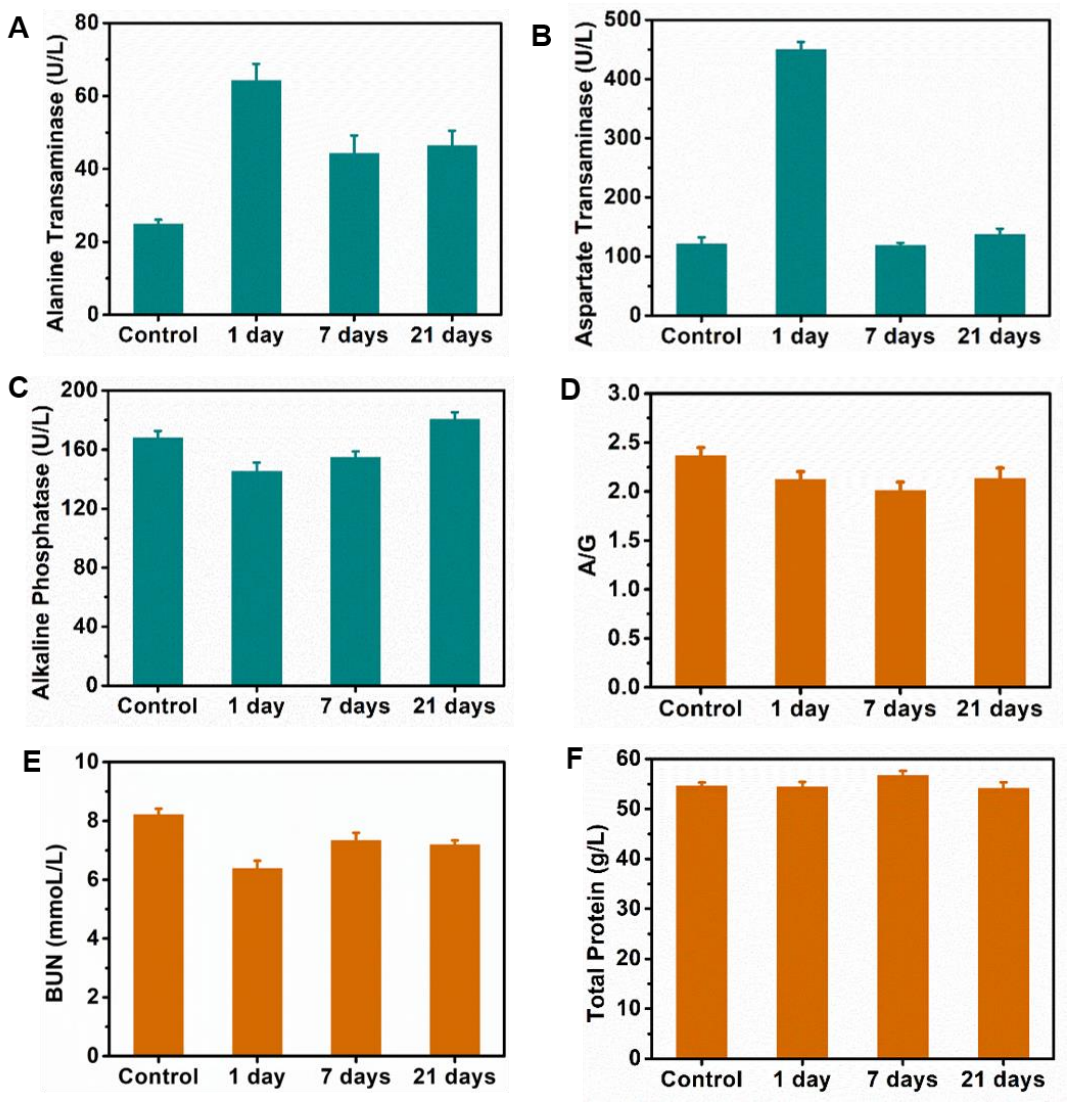

Figure S23. *In vivo* long-term toxicity assessments of ScNP-PEG. (A-F) Blood biochemistry at 0, 1, 7 and 21 days after *i.v.* injecting 25 mg kg^{-1} of ScNP-PEG.

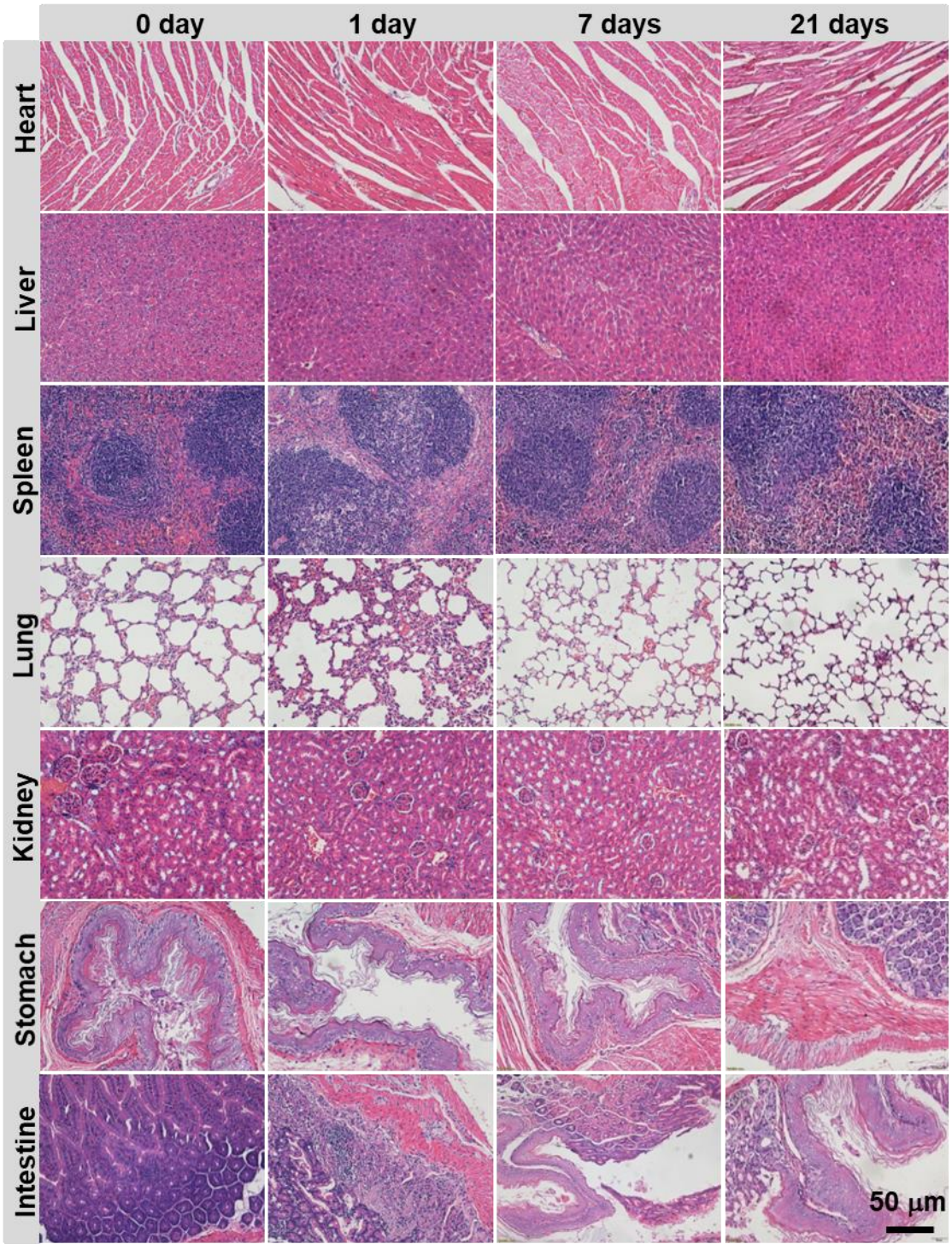

Figure S24. *In vivo* long-term toxicity assessments of ScNP-PEG. H&E-stained tissue sections of major organs including heart, liver spleen, lung, kidney, stomach and intestine from the mice treated with 25 mg kg^{-1} of ScNP-PEG at 0, 1, 7, and 21 days and untreated healthy mice were as control.