Electronic Supplementary Information

Synthesis of functionalized triple-doped zinc gallogermanate nanoparticles with superlong near-infrared persistent luminescence for long-term oral administrated bioimaging

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Supplementary Methods

Chemicals and materials. All reagents were of the highest available purity and at least of analytical grade. Ultrapure water (Wahaha, Hangzhou, China) was used throughout all experiments. $Zn(NO_3)_2 \cdot 6H_2O$ (99.99%), Ga_2O_3 (99.99%), GeO_2 (99.999%), $Cr(NO_3)_3 \cdot 9H_2O$ (99.99%), $Yb(NO_3)_3 \cdot 5H_2O$ (99.9%), $Er(NO_3)_3 \cdot 5H_2O$ (99.9%), γ-aminopropyltriethoxysilane (APTES, 99%), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl), N-hydroxysuccinimide (NHS), dimethyl sulfoxide (DMSO) and 4-dimethylaminopyridine (DMAP) were all purchased from Aladdin (Shanghai, China). Cetyltrimethyl ammonium bromide (CTAB) was purchased from Sinopharm Chemical Reagent (Beijing China). $NH_3 \cdot H_2O$, NaOH and ethanol were both obtained from Guangfu Fine Chemical Research Institute (Tianjin, China). All the glassware was cleaned with aqua regia ($HCl:HNO_3$ = 3:1, v/v) and thoroughly rinsed with ultrapure water before use.

Characterization. XRD patterns were acquired on a D/max-2500 diffractometer (Rigaku, Japan) equipped with Cu Kα radiation (λ = 1.5418 Å). The morphology and microstructure of the prepared ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was characterized by high-resolution transmission electron micrograph (HRTEM) on a JEM-2100F field emission transmission electron microscope (JEOL, Japan) operating at a 200 kV accelerating voltage. The samples were obtained by drying sample droplets on a 300-mesh Cu grid coated with a lacey carbon film. Photoluminescence and excitation spectra, and the time decay curves were recorded on a F-4500 spectrofluorometer (Hitachi, Japan) equipped with both continuous (450 W) and pulsed xenon lamps or hydrogen lamps. The phosphorescence signals were detected using the Hamamatsu PMT detectors (R928 and R5509-72). All the measurements were carried out at room temperature. The

photoluminescence quantum yield of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was obtained on an FLS920 spectrometer with an integration sphere attachment under excitation of 254 nm (Edinburgh, UK).

Fourier transform infrared spectra (FT-IR, 4000-400 cm^{-1}) in dry KBr were acquired on a Magna-560 spectrometer (Nicolet, Madison, WI). X-ray photoelectron spectroscopy measurements were carried out on a Axis Ultra DLD spectrometer fitted with a monochromated Al Kα X-ray source (hν = 1486.6 eV), hybrid (magnetic/electrostatic) optics, and a multichannel plate and delay line detector (Kratos Analytical, Manchester, UK). Thermogravimetric-differential thermal analysis (TG-DTA) was performed on a Rigaku Thermo plus EVO2 TG8121 analyzer (Netzsch, Germany) in air flow from 25 to 1400 °C with a heating rate of 15 °C min^{-1}.

The microscopic images were obtained on an IX81 motorized inverted microscope (Olympus, Japan). NIR afterglow decay images were recorded on a Berthold NightOWL LB 983 Imaging System (Bad Wildbad, Germany) equipped with CCD camera. *In vivo* fluorescence images of the mice were obtained with a NightOWL LB 983 *in vivo* Imaging System (Bethold, Bad Wildbad, Germany). The excitation filter was set as 530 nm, and the emission filter was set as 700 nm. Phosphorescence images were recorded by the CCD camera with constant exposure time. *In vitro* cytotoxicity of the probe was assessed using the cell counting assay, and cell numbers were counted with a Coulter Particle Size Analyzer (Beckman Coulter, High Wycombe, UK). The elemental analysis was performed by inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7500CX). Persistent luminescence nanoparticles were pre-excited with a UV lamp (254 nm, 6W) or red LED light (650 nm, 5,000 lm).

Preparation of ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. ZGGO:Cr^{3+},Yb^{3+},Er^{3+} nanoparticles were synthesized by a hydrothermal method in combination with calcination in air. Various volumes of the aqueous

solutions of chromium nitrate (0.1 M), zinc nitrate (0.1 M), yttrium nitrate (0.1 M), erbium nitrate (0.1 M) and ammonium germanate (0.1 M) were added to the aqueous solution of gallium nitrate (0.3 M) according to the chemical formula of $Zn_{1+x}Ga_{2-2x}Ge_xO_4$:2y%Cr^{3+},10y%Yb^{3+},y%Er^{3+} under vigorous stirring. 16 mg cetyltrimethyl ammonium bromide (CTAB) was then added to the reaction mixture, ammonia solution (30 wt%) was added to adjust the pH to 8.0. The reaction solution was ultrasonicated at room temperature for 20 min, and kept stirring for 1 h. The turbid solution was transferred into a 30 mL teflon-lined stainless steel autoclave, heated at 120 °C for 15 h, and then cooled to room temperature. The resulting compound was washed sequentially with ultrapure water and ethanol, and then lyophilized. The dried white powder was finally sintered in air at 1000 °C for 1.5 h. The as-synthesized ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was mixed with an ammonium aqueous solution (pH 9) under ultrasonication for 3 h. The mixture was transferred into a 30 mL teflon-lined stainless steel autoclave and treated at 200 °C for 12 h. The as-synthesized ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was washed with ultrapure water and lyophilized.

Hydroxylation was performed by ultrasonic treatment of the ZGGO:Cr^{3+},Yb^{3+},Er^{3+} powder (1000 mg) in 5 mM NaOH solution for 3 h. The resulting suspension was then vigorously stirred overnight at room temperature. The resulting colloid solution was centrifuged at 4500 rpm for 5 min. The resulting supernatant was collected and concentrated, and centrifuged at 3500 rpm for 20 min, ZGGO:Cr^{3+},Yb^{3+},Er^{3+} with a diameter of 40 nm were thus obtained in the supernatant.

Surface functionalization of ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. 5 mg hydroxylated ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was dispersed in dimethylformamide (DMF, 2 mL) under sonication, to which γ-aminopropyltriethoxysilane (APTES, 20 μL) was added under stirring at 80 °C for 24 h. The resulting particles were collected by centrifugation, and washed with DMF to remove the

unreacted APTES. Thus, NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was obtained. To conjugate FA to NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}, 10 mg of NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was dispersed in dichloromethane (10 mL) under sonication, then dimethyl sulfoxide (DMSO, 10 mL), FA (8 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl, 5 mg), N-hydroxysuccinimide (NHS, 10 mg) and 4-dimethylaminopyridine (DMAP, 10 mg) were sequentially added into the mixture. The mixture was gently stirred in the dark at room temperature for 48 h. The unreacted FA was removed by centrifugation and the resulting FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was washed three times with ultrapure water.

Cytotoxicity Assay. *In vitro* cytotoxicity of the ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was assessed using a cell counting assay. Cell numbers were counted with a Coulter Particle Size Analyzer (Beckman Coulter, High Wycombe, UK). Mouse embryo fibroblast cell lines (Balb/3T3) and HeLa cell lines obtained from China Center for Type Culture Collection (Wuhan, China) were cultured in Dulbecco's modified Eagle's high glucose medium (DMEM) supplemented with 10% fetal bovine serum (FBS). MCF-7 cell lines obtained from the Cell Culture Center (IBMS, CAMS/PUMC) (Peking, China) were cultured in MEM Eagles with Earle's Balanced Salts (MEM-EBSS). 3T3 cell lines, HeLa cell lines and MCF-7 cell lines were plated at a density of 4×10^4 cells per well in 64-well plates, and grown for 24 h at 37°C in 5% CO_2. The NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} dispersed in 10 mM PBS solution with a wide concentration range from 10 to 640 μg mL^{-1} were subsequently added into the cell and incubated for another 24 h under the same conditions as above. The cells were then washed with 10 mM PBS (pH 7.4), trypsinized with 200 μL trypsin/EDTA solution, and resuspended to a final volume of 1 mL cell medium for further measurement of cell viability by a cell counting chamber.

Animal Model. All animal experiments were conducted in accordance with guidelines of the Tianjin Committee of Use and Care of Laboratory Animals, and all project protocols were approved by the Animal Ethics Committee of Nankai University. All animal procedures were treated with chloral hydrate anaesthesia (200 μL, 4%) and all efforts were made to minimize suffering. The adult athymic Balb/c nude mice (15~20 g) were obtained from Beijing HFK bioscience Co., LTD (Beijing, China). The subcutaneous MCF-7 tumor mice model was established by subcutaneously injecting 5×10^6 tumor cells in nude mice. The tumor carrying mice were used on 10 days after injection.

Histopathology. The histological changes in the main organs of mice gavaged with FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} (0.8 mL, 2.0 mg mL^{-1}) were observed 14 days after oral administration. The selected organs (heart, liver, spleen, lung, kidney, pancreas, intestine, and stomach) were fixed in 10% neutral buffered formalin，embedded in paraffin, sectioned (5μm thick), and stained with hematoxylin and eosin (H&E). The histological sections were observed under an optical microscope.

Comparison of NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} and FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} for oral administrated *in vivo* imaging. *In vivo* experiments were performed on anesthetized mice with chloral hydrate (150 μL, 4%). 0.4 mg of NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} and FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} solution (0.2 mL, 2 mg mL^{-1} in physiological saline (0.9% NaCl aqueous solution)) were given to MCF-7 tumor bearing mice via oral administration with gavage needle, with a first *ex vivo* excitation for 5 min under 4 W 254 nm UV lamp. The nude mouse were fasted for 36 h before oral administration of materials.

Comparison of oral administration and intravenous injection for *in vivo* imaging with FA-

ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. *In vivo* experiments were performed on anesthetized mice with chloral hydrate (150 μL, 4%). 0.3 mg of FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} solution (0.15 mL, 2 mg mL^{-1} in physiological saline (0.9% NaCl aqueous solution)) were given to MCF-7 tumor bearing mice via oral administration and tail vein intravenous injection, respectively, after a first *ex vivo* excitation under 4 W 254 nm UV lamp for 5 min. The nude mouse were fasted for 36 h before oral administration of materials. 120 min, 8 h, and 24 h after injection, the mice were excited with a red LED light (650 ± 10 nm) for 60 s to reactivate the persistent luminescence of FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}, and the signal acquisition was resumed under the optima camera.

Long-term biodistribution analysis. The FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} (0.4 mL, 2 mg mL^{-1}) were given to MCF-7 tumor-bearing mice via oral administration and tail vein intravenous injection, respectively. The nude mouse were fasted for 36 h before oral administration of materials. The mice were sacrificed and major organs were collected for *ex vivo* biodistribution analysis. Mice were euthanized humanely via chloral hydrate anaesthesia (200 μL, 4%) 24 h after administration of ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. Necropsies were performed for collecting major organs and tissues (stomach, intestinal tract, liver, kidney, spleen, and tumor). The tissues were weighed and dissolved in aqua regia for two weeks, then diluted 2000× in water and submitted for ICP-MS analysis. The %ID/gram values of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} in all analyzed organs were determined by comparing the Ga concentration, giving a quantitative measure of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} biodistribution.

Supplementary Tables 1-2

Table S1. Studied sample compositions of the $Zn_{1+x}Ga_{2-2x}Ge_xO_4$:2y%Cr^{3+},10y%Yb^{3+},y%Er^{3+} solid solutions

y value	x value	Composition	Name
0.05	0	$ZnGa_2O_4$:0.1%Cr^{3+},0.5%Yb^{3+},0.05%Er^{3+}	A 1
	0.1	$Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:0.1%$Cr^{3+}$,0.5%$Yb^{3+}$,0.05%$Er^{3+}$	A 2
	0.25	$Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4$:0.1%$Cr^{3+}$,0.5%$Yb^{3+}$,0.05%$Er^{3+}$	A 3
	0.5	$Zn_{1.5}GaGe_{0.5}O_4$:0.1%Cr^{3+},0.5%Yb^{3+},0.05%Er^{3+}	A 4
0.14	0	$ZnGa_2O_4$:0.28%Cr^{3+},1.4%Yb^{3+},0.14%Er^{3+}	B 1
	0.1	$Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:0.28%$Cr^{3+}$,1.4%$Yb^{3+}$,0.14%$Er^{3+}$	B 2
	0.25	$Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4$:0.28%$Cr^{3+}$,1.4%$Yb^{3+}$,0.14%$Er^{3+}$	B 3
	0.5	$Zn_{1.5}GaGe_{0.5}O_4$:0.28%Cr^{3+},1.4%Yb^{3+},0.14%Er^{3+}	B 4
0.25	0	$ZnGa_2O_4$:0.5%Cr^{3+},2.5%Yb^{3+},0.25%Er^{3+}	C 1
	0.1	$Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:0.5%$Cr^{3+}$,2.5%$Yb^{3+}$,0.25%$Er^{3+}$	C 2
	0.25	$Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4$:0.5%$Cr^{3+}$,2.5%$Yb^{3+}$,0.25%$Er^{3+}$	C 3
	0.5	$Zn_{1.5}GaGe_{0.5}O_4$:0.5%Cr^{3+},2.5%Yb^{3+},0.25%Er^{3+}	C 4
0.50	0	$ZnGa_2O_4$:1.0%Cr^{3+},5.0%Yb^{3+},0. 5%Er^{3+}	D 1
	0.1	$Zn_{1.1}Ga_{1.8}Ge_{0.1}O_4$:1.0%$Cr^{3+}$,5.0%$Yb^{3+}$,0. 5%$Er^{3+}$	D 2
	0.25	$Zn_{1.25}Ga_{1.5}Ge_{0.25}O_4$:1.0%$Cr^{3+}$,5.0%$Yb^{3+}$,0. 5%$Er^{3+}$	D 3
	0.5	$Zn_{1.5}GaGe_{0.5}O_4$:1.0%Cr^{3+},5.0%Yb^{3+},0. 5%Er^{3+}	D 4

Table S2. The effect of preparation process on the quantum yield of the PLNPs materials

Sample	Hydrothermal	Calcination	Quantum yield (%)
ZGGO:Cr^{3+}	120°C 15 h	1000°C 1.5 h	3.69
ZGGO:Cr^{3+},Yb^{3+}	120°C 15 h	1000°C 1.5 h	3.12
ZGGO:Cr^{3+},Er^{3+}	120°C 15 h	1000°C 1.5 h	1.73
ZGGO:Cr^{3+},Yb^{3+},Er^{3+}	120°C 15 h	1000°C 2.5 h	9.43
	120°C 15 h	1000°C 2 h	9.76
	120°C 15 h	1000°C 1.5 h	9.89
	120°C 15 h	1000°C 1 h	10.2
	120°C 15 h	1000°C 0.5 h	7.92
	120°C 15 h	1000°C 0 h	5.27
	120°C 15 h	750°C 5 h	4.01
	120°C 15 h	-	0.41
	220°C 15 h	-	1.19

Supplementary Figures 1-14

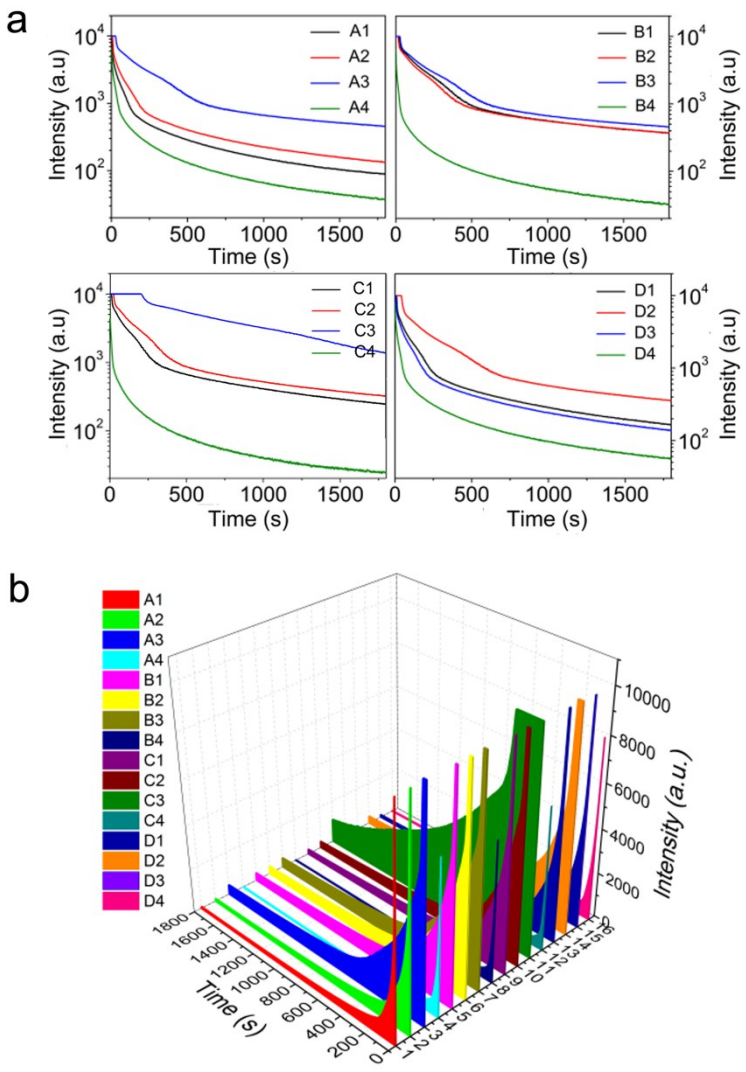

Fig. S1 The afterglow decay curves of $Zn_{1+x}Ga_{2-2x}Ge_xO_4$:2y%Cr^{3+},10y%Yb^{3+},y%Er^{3+}powder after 5-min irradiation with a 254 nm UV lamp. (a) Two-dimensional graphs. (b) Three-dimensional graphs. The compositions of the materials are listed in Table S1.

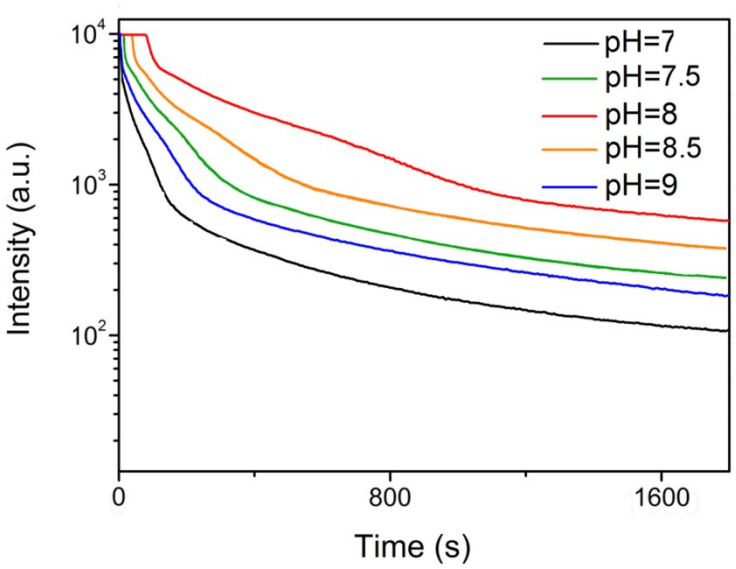

Fig. S2 NIR afterglow decay curve of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} prepared at different pH values of starting solution. The ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was firstly irradiated with a 4 W 254 nm UV lamp for 2 min before measurement. Persistent luminescence intensity was monitored at 691 nm as a function of time (logarithmic scale).

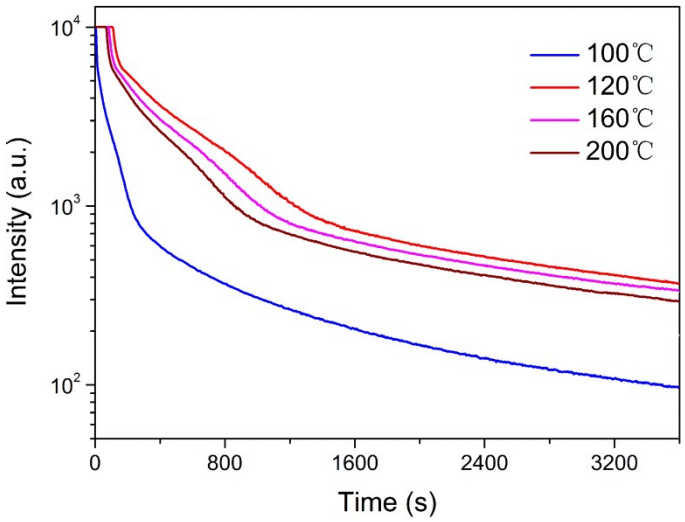

Fig. S3 NIR afterglow decay curve of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} synthesized under different hydrothermal temperature. The ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was firstly irradiated with a 4W 254 nm UV lamp for 2 min before measurement. Persistent luminescence intensity was monitored at 691 nm as a function of time.

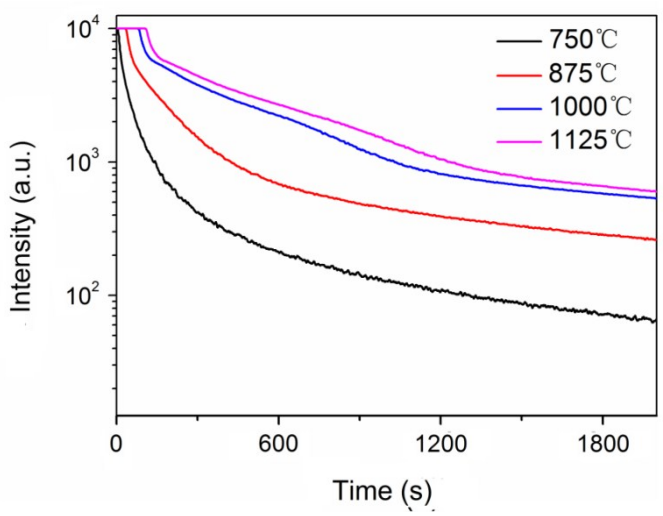

Fig. S4 The afterglow decay curves of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} powder synthesized under different calcination temperatures. The ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was firstly irradiated with a 4W 254 nm UV lamp for 2 min before measurement. Persistent luminescence intensity was monitored at 691 nm as a function of time. The NIR persistent luminescence of ZGGO:Cr3+,Yb3+,Er3+ increased with calcination temperature from 750 to 1000 ºC, but did not change obviously with further increase of calcination temperature to 1125 ºC.

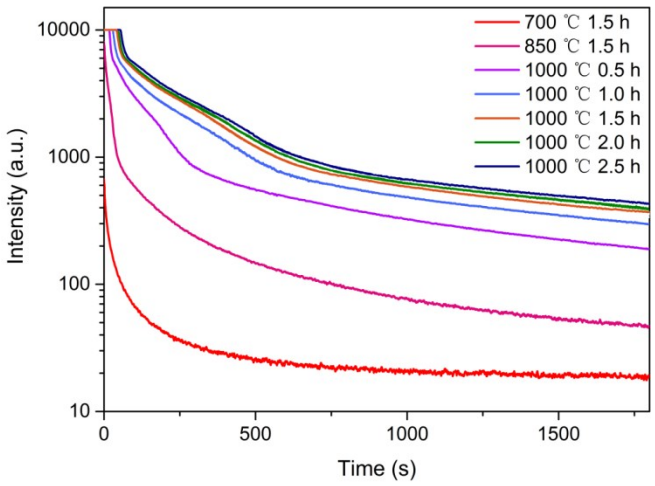

Fig. S5 The afterglow decay curves of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} powder synthesized with different calcination time. The ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was firstly irradiated with a 4W 254 nm UV lamp for 2 min

before measurement. Persistent luminescence intensity was monitored at 691 nm as a function of time. The measurement range of the instrument is 0-10000, the signal beyond the range appear to be the platform.

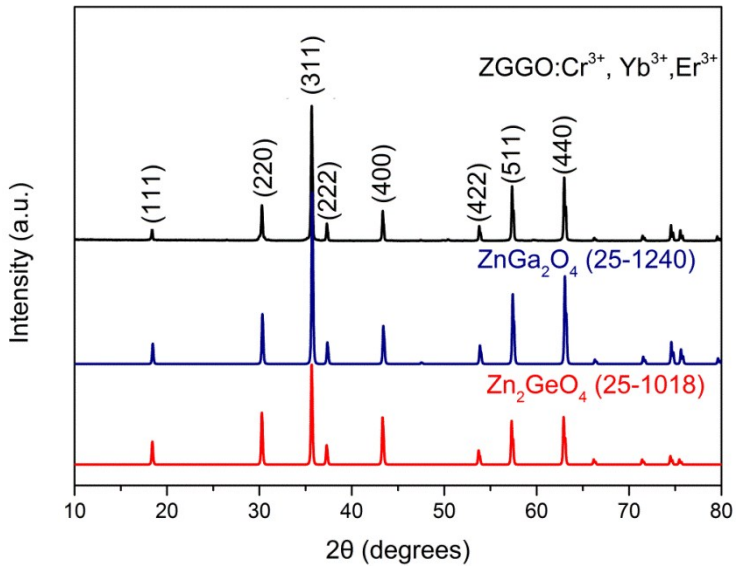

Fig. S6 The XRD patterns of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} powder.

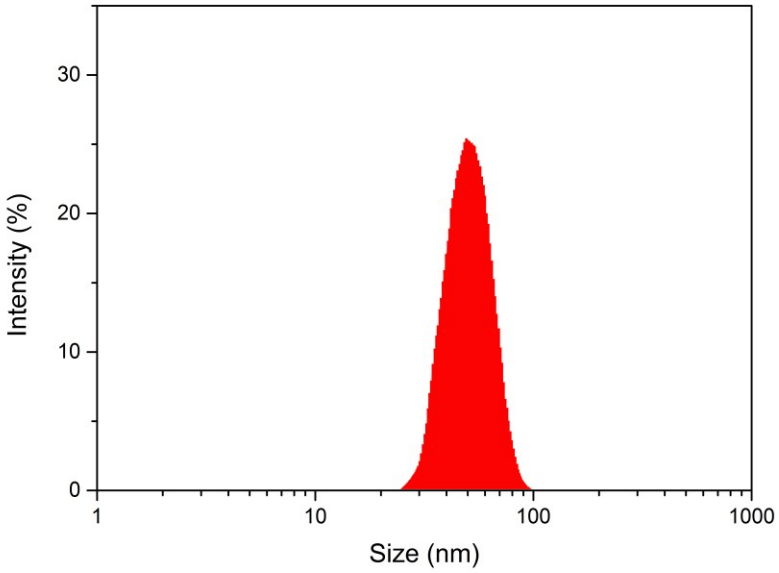

Fig. S7 Dynamic light scattering spectra of ZGGO:Cr^{3+},Yb^{3+},Er^{3+}.

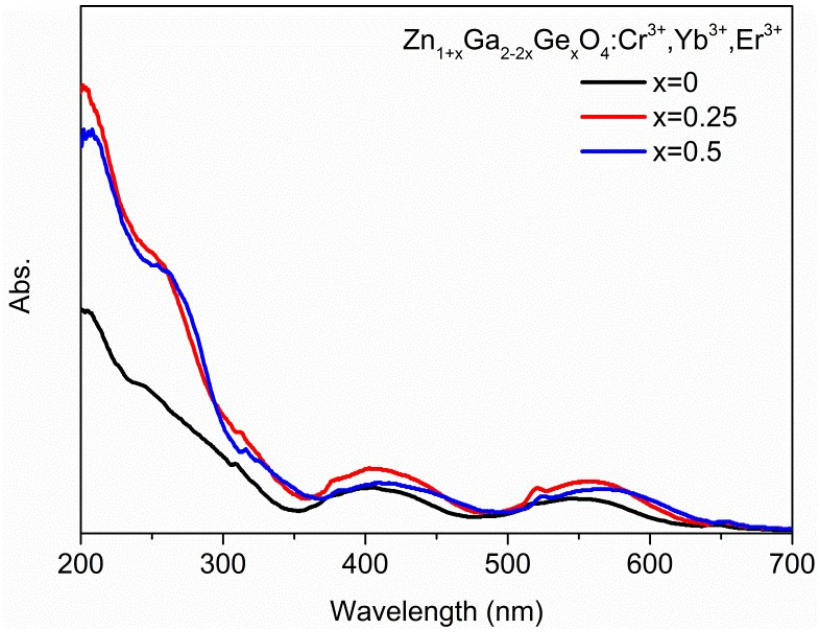

Fig. S8 UV-vis absorption spectra of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} with different Ge substitution amount.

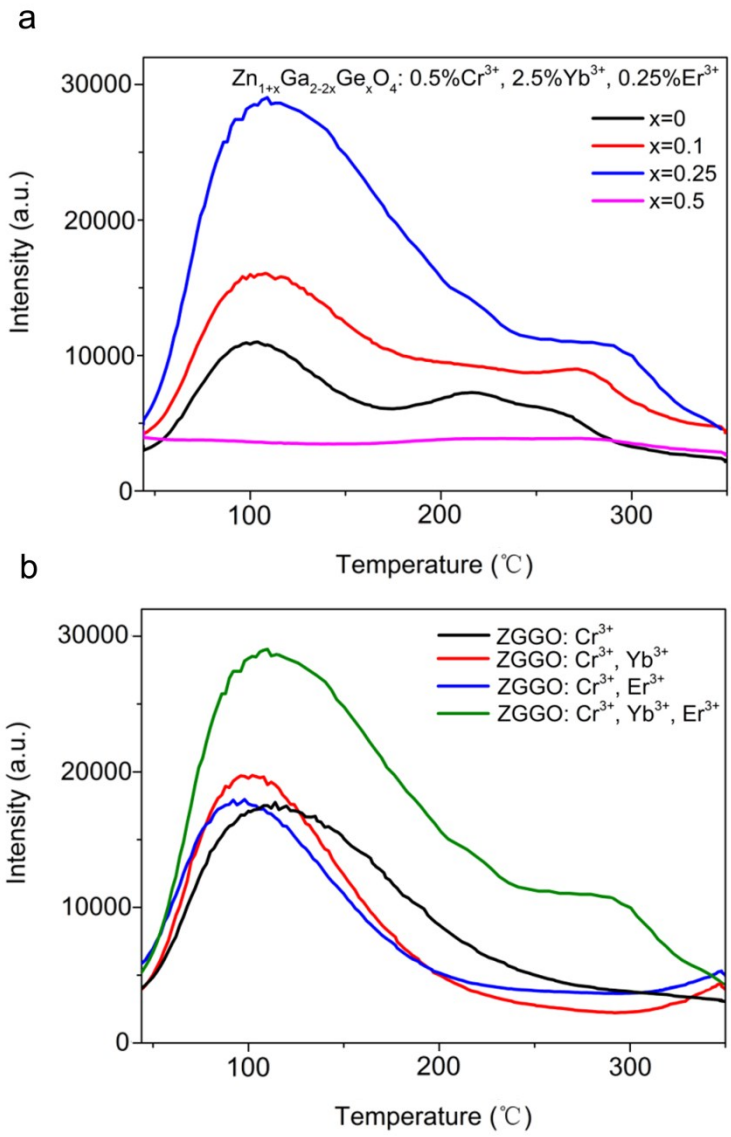

Fig. S9 Thermoluminescence glow curves of the Cr^{3+} emission in the $Zn_{1+x}Ga_{2-2x}Ge_xO_4$:2y%Cr^{3+},10y%Yb^{3+},y%Er^{3+} phosphors. (a) Effect of Ge substitution. (b) Effect of co-doping. The samples were first cooled down to 100 K (-173 ºC) and exposed to 254 nm UV light for 5 min. After another 5 min of waiting time, the samples were heated up from 25 ºC to 350 ºC with a heating rate of 2 °C s^{-1}

Notes: As shown in Supplementary Fig. 9a, the intensity of both the low-temperature band (30-150 °C) and high-temperature band (150-350°C) of $Zn_{1+x}Ga_{2-2x}Ge_xO_4$:0.5%Cr^{3+},2.5%Yb^{3+},0.25%Er^{3+} increased with the Ge content increase from x =

0 to x = 0.25, and then decreased with further increase to x = 0.5. The two bands have the strongest intensity at x = 0.25, especially the low temperature band. The density of shallow traps increased due to the higher ionization energy (3302 kJ mol^{-1}) of germanium ion than that of gallium ion (2963 kJ mol^{-1}) in the matrix. Further increase of the Ge content to x = 0.5 made the TL signal drop significantly. The above results indicate that x = 0.25 is the most suitable substitution amount of Ge in the matrix.

As shown in Supplementary Fig. 9b, ZGGO:Cr^{3+}, ZGGO:Cr^{3+},Yb^{3+}, and ZGGO:Cr^{3+},Er^{3+} gave an asymmetry broad TL band between 30 ºC and 350 ºC with a peak at 110 ºC, however, ZGGO:Cr^{3+},Yb^{3+},Er^{3+} exhibited much stronger TL intensity than ZGGO:Cr^{3+}, ZGGO:Cr^{3+},Yb^{3+}, ZGGO:Cr^{3+},Er^{3+} in the temperature range studied, indicating co-doping of Yb^{3+} and Er^{3+} led to the increase of trap density. Furthermore, the TL spectra of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} not only show a predominate low temperature band at 120 ºC, but also a relatively weak band at 280 ºC. The above results show that the co-doped Yb^{3+} and Er^{3+} ion couple not only introduced more density of trap centers, but also produced new deep traps to improve the long lasting photoluminescence process.

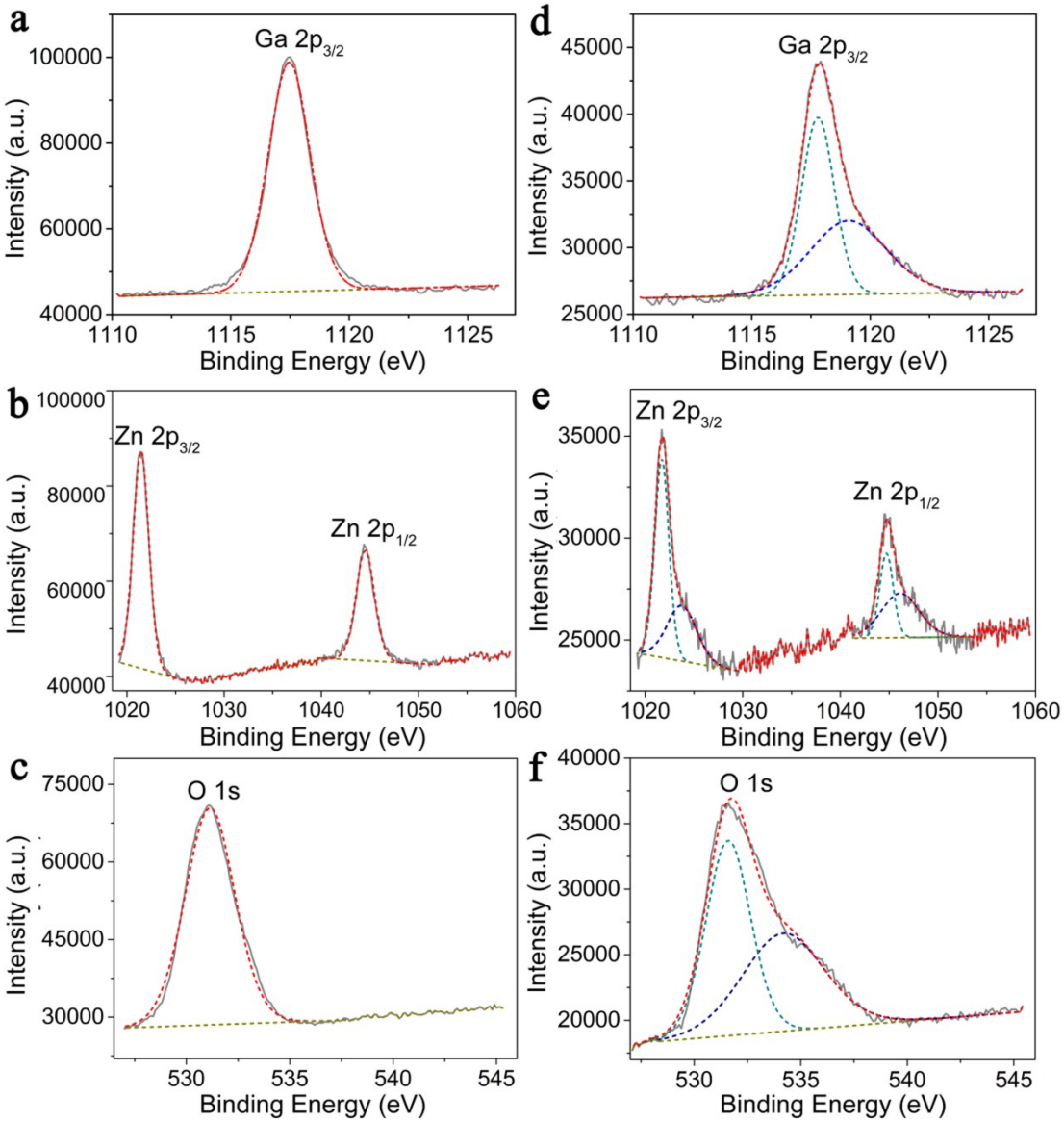

Fig. S10 XPS spectra of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} synthesized before and after calcination (the gray solid, red dash, olive drab dash, and cyan and navy blue dash lines refer to the experimental data, the fitted data, the background signal and overlapping peaks, respectively); (**a**) Ga-2p line before calcination. (**b**) Zn-2p line before calcination. (**c**) O-1s line before calcination. (**d**) Ga-2p line after 1 h calcination at 1000 ^{o}C. (**e**) Zn-2p line after 1 h calcination at 1000 ^{o}C. (**f**) O-1s line after 1 h calcination at 1000 ^{o}C.

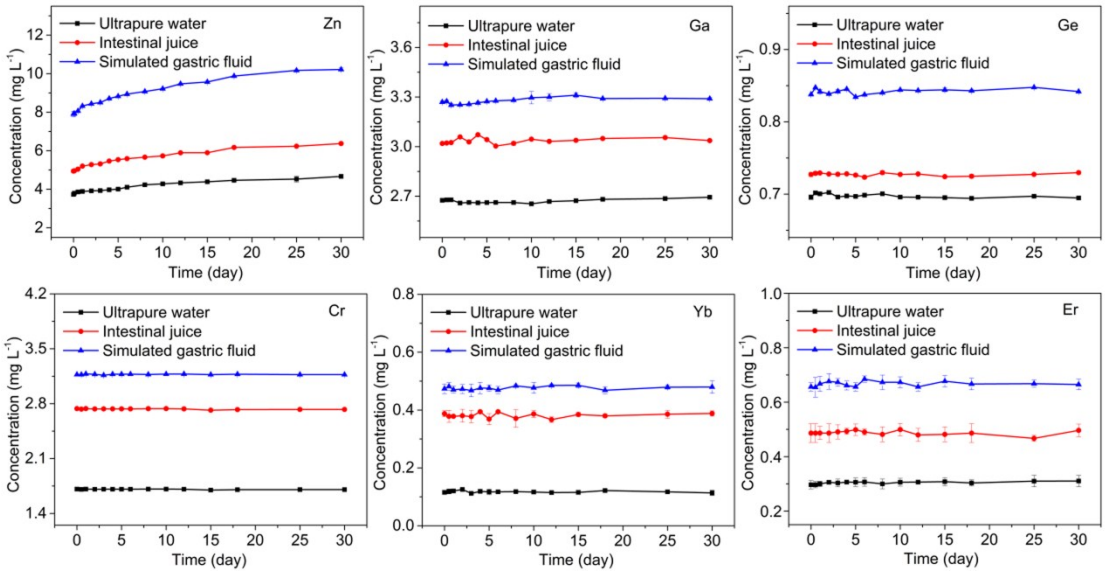

Fig. S11 Evaluation of the composition stability of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} in different media.

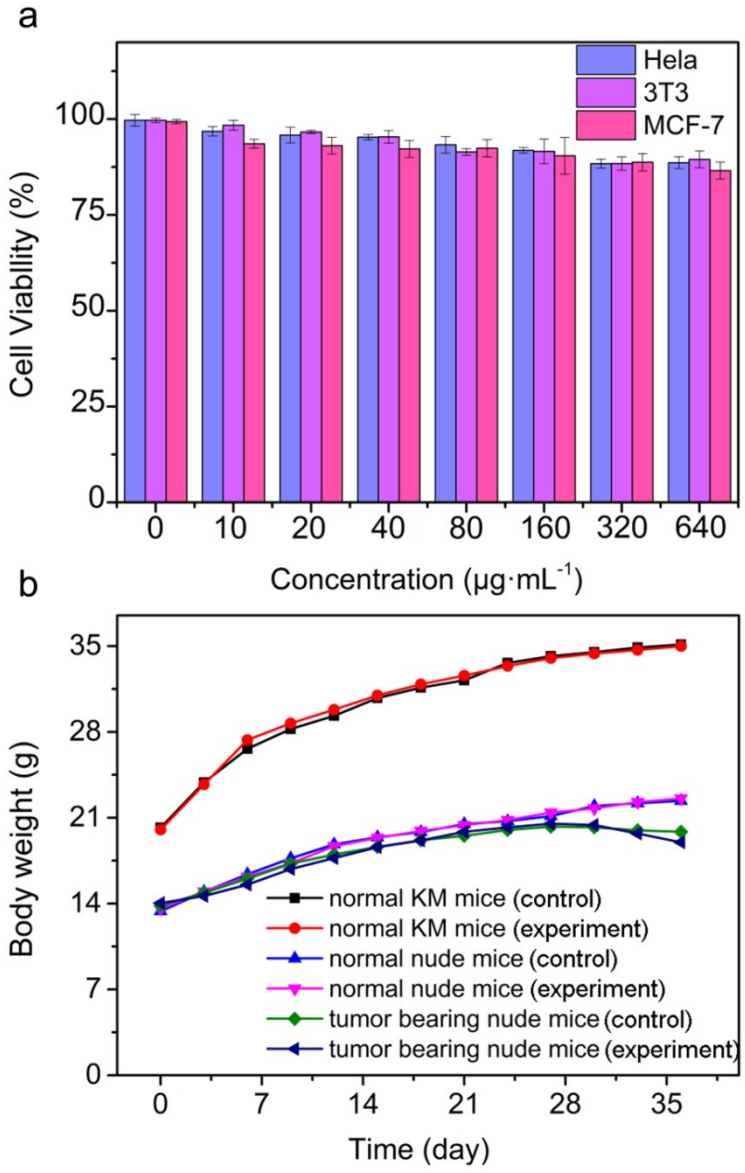

Fig. S12 Toxicity of ZGGO:Cr^{3+},Yb^{3+},Er^{3+} and FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. (a) *In vitro* cell viability of 3T3 cells，MCF- 7 cells and HeLa cells incubated with ZGGO:Cr^{3+},Yb^{3+},Er^{3+} nanoparticles at different concentrations for 24 h. The error bars represent standard deviation. (**b**) Body weight changes of the mice (normal KM mice, normal nude mice and MCF-7 tumor bearing nude mice). The imaging probes (FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}: 0.8 mL, 2.0 mg mL^{-1}) were given to rats via oral administration. The control mouse was intragastric administrated with saline.

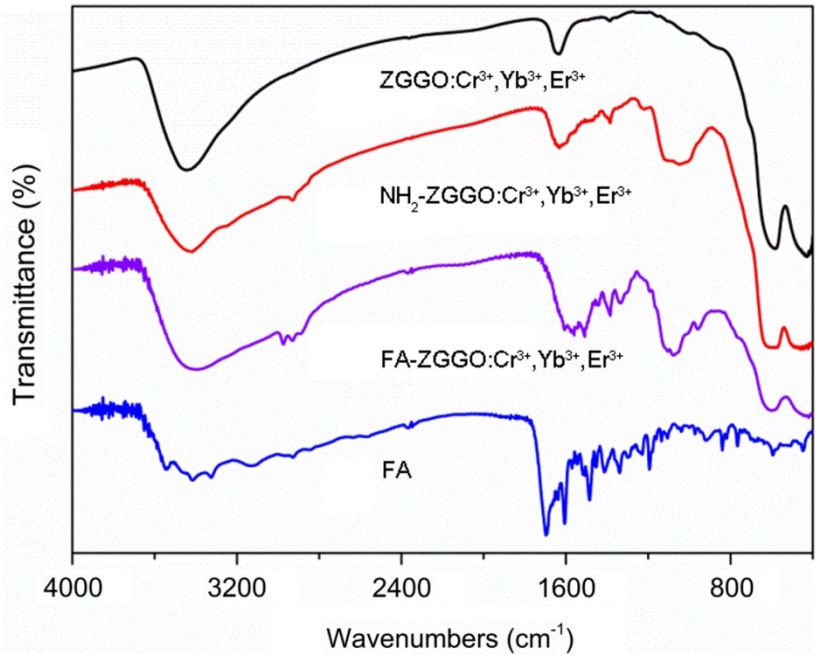

Fig. S13 Infrared spectroscopy spectra of ZGGO:Cr^{3+},Yb^{3+},Er^{3+}, NH_2-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}, and FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} and folate (FA).

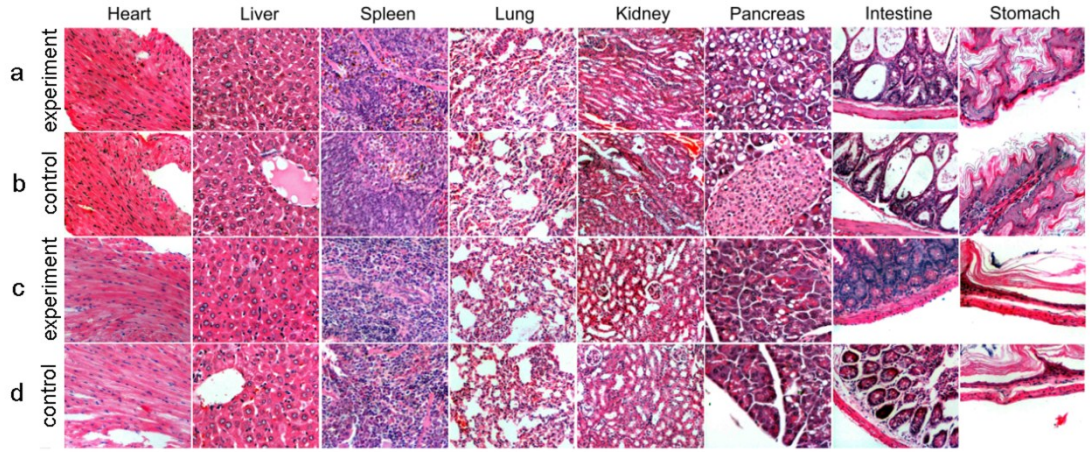

Fig. S14 Representative H&E stained images of major organs including heart, liver, spleen, lung, kidney, pancreas, intestine, and stomach. (a) Normal nude mouse treated with FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. (b) Normal nude mouse treated with saline. (c) MCF-7 tumor-bearing mouse treated with FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+}. (d) MCF-7 tumor-bearing mouse treated with saline. In the experiment groups FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} (0.8 mL, 2.0 mg mL^{-1}) were given to mice (n=3)

by gavage. In the control groups, saline (0.9% NaCl 0.8 mL) was given to mice (n=3) by gavage. The H&E stain was preceded 14 days after administration. The scale bars is 50 μm for all images.

Notes: The *in vivo* toxicity of FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was evaluated via monitoring histological changes in several susceptible organs including heart, liver, spleen, lung, and kidney to show whether FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} could cause any harmful effect during retention in the mouse body for 14 days. The results show that no significant evidence for organ damage or inflammatory lesion associated with the administration of FA-ZGGO:Cr^{3+},Yb^{3+},Er^{3+} was detected.