

## Supplementary Information

### **Component-optimized chemo-dynamic nanoagent for enhanced tumor cell-selective chemo-dynamic therapy with minimal side effect in glioma mouse model**

Lihong Qiao <sup>a†</sup>, Xiaoxia Li <sup>a†</sup>, Yuanqiang Xiao<sup>a</sup>, Jianming Yuan<sup>a</sup>, Dongsheng Yu <sup>a</sup>,  
Mingxiang Zuo <sup>a</sup>, Jifeng Chen <sup>a</sup>, Shisong Han <sup>a</sup>, Du Cheng <sup>a\*</sup>

<sup>a</sup>Key Laboratory for Polymeric Composite & Functional Materials of Ministry of Education, School of Materials Science and Engineering, Sun Yat-sen University, Guangzhou 510275, P. R. China.

\* Correspondence should be addressed to:

Du Cheng

Tel.: +86-20-84112172

Fax: +86-20-84112172

E-mail:chengdu@mail.sysu.edu.cn

†These authors contributed equally to this work.

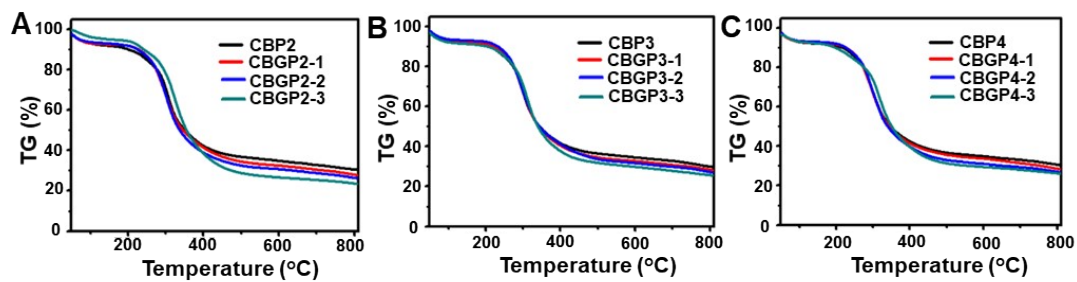
## **Materials**

### Chemical reagents

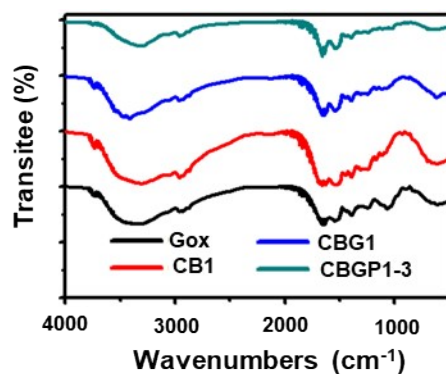
Glucose oxidase (Gox, 200 units/mg) and bovine serum albumin (BSA) were obtained from Shanghai Macklin Biochemical Co., Ltd. cupric chloride dihydrate ( $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), fluorescein isothiocyanate (FITC), PEG<sub>2k</sub>-PEI<sub>1.8k</sub>, 5,5-Dimethyl-1-pyrroline N-oxide (DMPO), methylene blue (MB), glucose (Glu), 4',6-diamidino-2-phenylindole (DAPI) and Cy3.5-NHS were purchased from Aladdin Reagent Co. Ltd. (Shanghai), other reagents were purchased from Beijing Chemical Reagent Co. All the reagents were used without further treatment. C6 brain glioma cells and NSC neural stem cells purchased from the institute of biochemistry and cell biology, chinese academy of sciences, shanghai, China. All of the cells were grown in dulbecco's modified eagle's medium (DMEM, GIBCO) supplemented with 10% heat-inactivated fetal bovine serum (FBS, GIBCO), 100 U/mL penicillin and 100  $\mu\text{g}/\text{mL}$  streptomycin (Sigma), and the culture medium was replaced once every day.

### **Characterization**

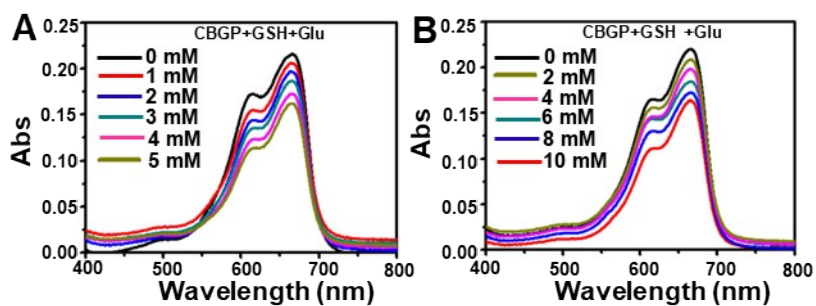
The morphology of nanoparticles was recorded by using a high-resolution transmission electron microscope (HR-TEM, FEI TECNAI G2, Germany) at 200 kV. Thermal Gravimetric Analyzer (TGA) were conducted 209F1 libra (Germany). X-ray photoelectron spectra (XPS) spectra were conducted on a Thermo Scientific ESCALAB 250 Multitechnique Surface analysis system (Thermo Electron Co., USA). Fourier Transform Infrared (FT-IR) spectra were recorded using a Bruker Vertex 70 spectrometer (Bruker, Billerica, MA). UV-vis absorption spectra were conducted using a UV-2450 spectrophotometer (Shimadzu, Japan). Sizes and zeta potentials of the nanoparticles were analyzed using a Zetasizer Nano-ZS (Malvern Instruments Ltd., UK). CLSM images were conducted on Zeiss LSM 780 imaging system (Carl Zeiss Inc., Jena, Germany). Flow cytometry assay was carried out on Becton Dickinson FACSAria sorting flow cytometer (Becton-Dickinson, Mountain View, US). Circular dichroism (CD) spectra were performed on a J-815 spectrometer (Jasco, Japan). Inductively coupled plasma-mass spectrometry (ICP-MS) were carried out on an Agilent 7700x series ICP-MS instrument (USA). Electron spin resonance (ESR) spectra were conducted on an EMXplus spectrometer (Bruker, Germany).



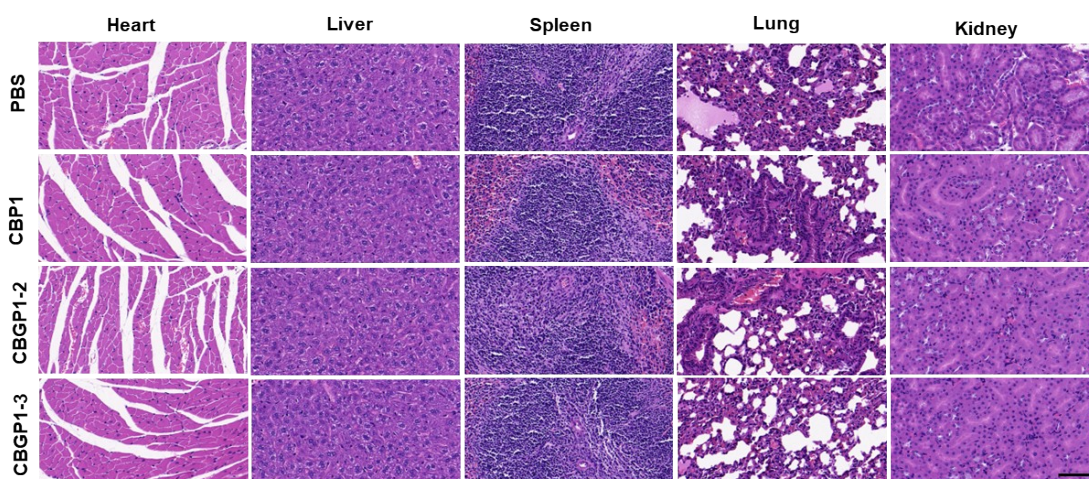
**Fig. S1** TGA spectra of (A) CBP2, CBGP2-1, CBGP2-2, and CBGP2-3 NPs, (B) CBP3, CBGP3-1, CBGP3-2, and CBGP3-3 NPs, and (C) CBP3, CBGP3-1, CBGP3-2, and CBGP3-3 NPs.



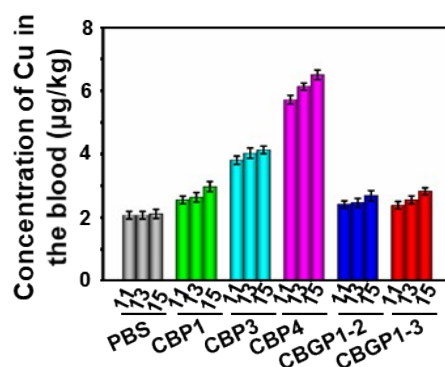
**Fig. S2** FT-IR of native Gox, CB1 nanocluster, CBG1 nanoparticles and CBGP1-3 nanoparticles.



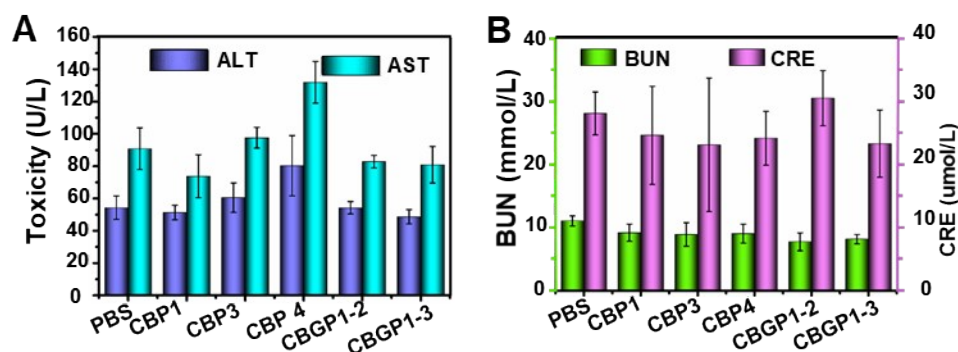
**Fig. S3** UV-vis absorption spectra of CBGP1-3 NPs solution containing MB under different concentrations of (A) GSH and (B) glucose (Glu). The concentration of CBGP1-3 NPs was 10  $\mu\text{g}/\text{mL}$ . The concentrations of GSH in the panel (A) and glucose in the panel (B) were 10 mM and 5 mM, respectively.



**Fig. S4** H&E staining images of the main organ (heart, liver, spleen, lung, and kidney) tissues isolated from the mice treated with PBS, CBP1, CBGP1-2 and CBGP1-3 NPs, respectively. The scale bar is 50  $\mu\text{m}$ .



**Fig. S5** Concentrations of copper in blood from mice treated with PBS, CBP1, CBP3, CBP4, CBGP1-2 and CBGP1-3 NPs at a concentration of 6 µg /mL at 5 d, 10 d and 15 d after first drug administration.



**Fig. S6** Blood biochemistry aspartate transaminase (AST), alanine aminotransferase (ALT), creatinine (CRE) and urea nitrogen (BUN) analyses of the mice bearing orthotopic C6-Luc tumor at 10 d after first drug administration. The mice were treated with PBS, CBP1, CBP3, CBP4, CBGP1-2 and CBGP1-3 NPs at a concentration of 6 µg/mL, respectively.