**Supporting Information** 

## Ultrasmall hybrid protein-copper sulfide nanoparticles for targeted photoacoustic imaging of orthotopic hepatocellular carcinoma with high signal-to-noise ratio

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Figure S1



Figure S1. The zeta potential distribution of (a) CuS@BSA-RGD NPs and (b) CuS@BSA NPs.

Figure S2



**Figure S2.** Cu 2p region X-ray photoelectron spectroscopy (XPS) spectra of (a) CuS@BSA-RGD NPs and (b) CuS@BSA NPs.

Figure S3



**Figure S3.** (a) The photograph of the normal mouse liver. (b) The ultrasound images of liver region in normal and HCC bearing mice. The red circle delineates the HCC region.

Figure S4



**Figure S4.** (a) The photograph of the normal and HCC bearing liver tissues. (b) The HE stained images of HCC bearing liver tissues. The red dotted square delineates the HCC region.

Figure S5



Figure S5. In vivo PA imaging of CuS@BSA NPs in orthotopic liver cancer model.

## Figure S6



**Figure S6.** (a and b) Photograph and corresponding PA MAP image of liver in HCC bearing mouse. (c) The B-scan of white dash line region in (b). (d and e) Photograph and corresponding PA MAP image of normal liver. (f) The comparison of PA signals between health liver region and HCC region. (scale bar: 10 mm).

Figure S7



**Figure S7.** The amount of Cu in liver and tumor at 24 h post CuS@BSA-RGD NPs injection.



Figure S8. Blood circulation profile of CuS@BSA-RGD NPs.