Ultrasmall Au $_{10-12}$(SG) $_{10-12}$ Nanomolecules for High Tumor Specificity and Cancer Radiotherapy

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Introduction

❑ Radiotherapy has been considered as part of the treatment regime following tumor surgical removal. It has high efficiency as up to 50% patients are treated with radiotherapy during their battle against cancer.

❑ In spite of that, high energy radiation during the treatment not only kills tumor cells but also destroys healthy cells along with them, leading to unavoidable damage to normal tissues.

❑ Localizing and controlling the radiation dose can maximize tumor eradication and minimize side effects.

❑ Conventional drug-based radiosensitizers while are efficient at the site of the tumor do not have any targeting capabilities and depend heavily on precise localization of the drug to the tumor cells.

❑ Sometimes for very small tumors with dispersed distribution within a tissue, it becomes impossible to avoid the interspersed normal tissues while only affecting the tumor cells.

❑ The use of radiosensitizers to increase the local treatment efficiency under a relatively low and safe radiation dose is the most promising solution to address this challenge.

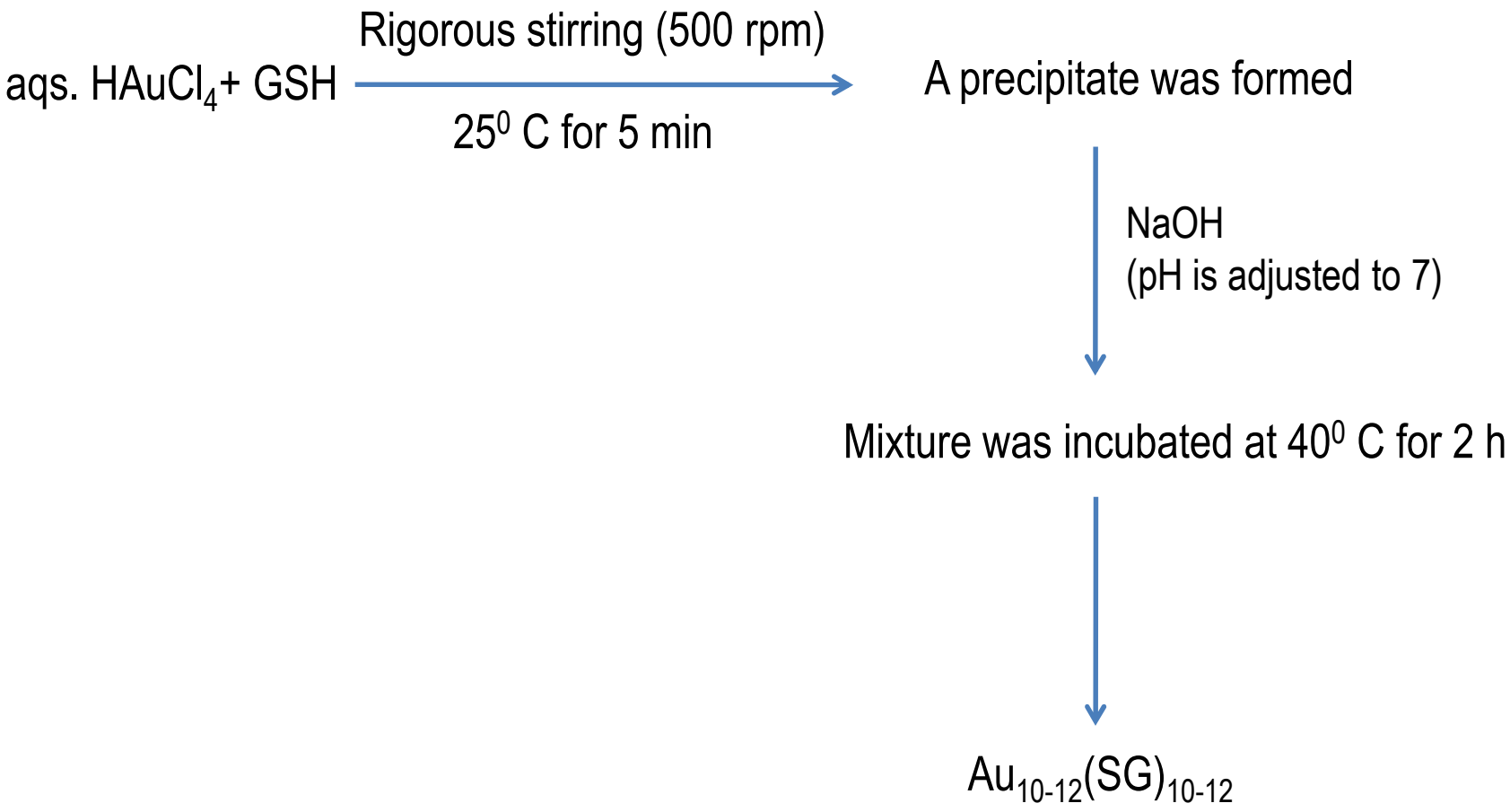
❑ An ideal radiosensitizer should have high radiotherapy enhancement, good tumor targeting capability, good biocompatibility, and efficient renal clearance to avoid potential short- and longterm detrimental effects on the patient.

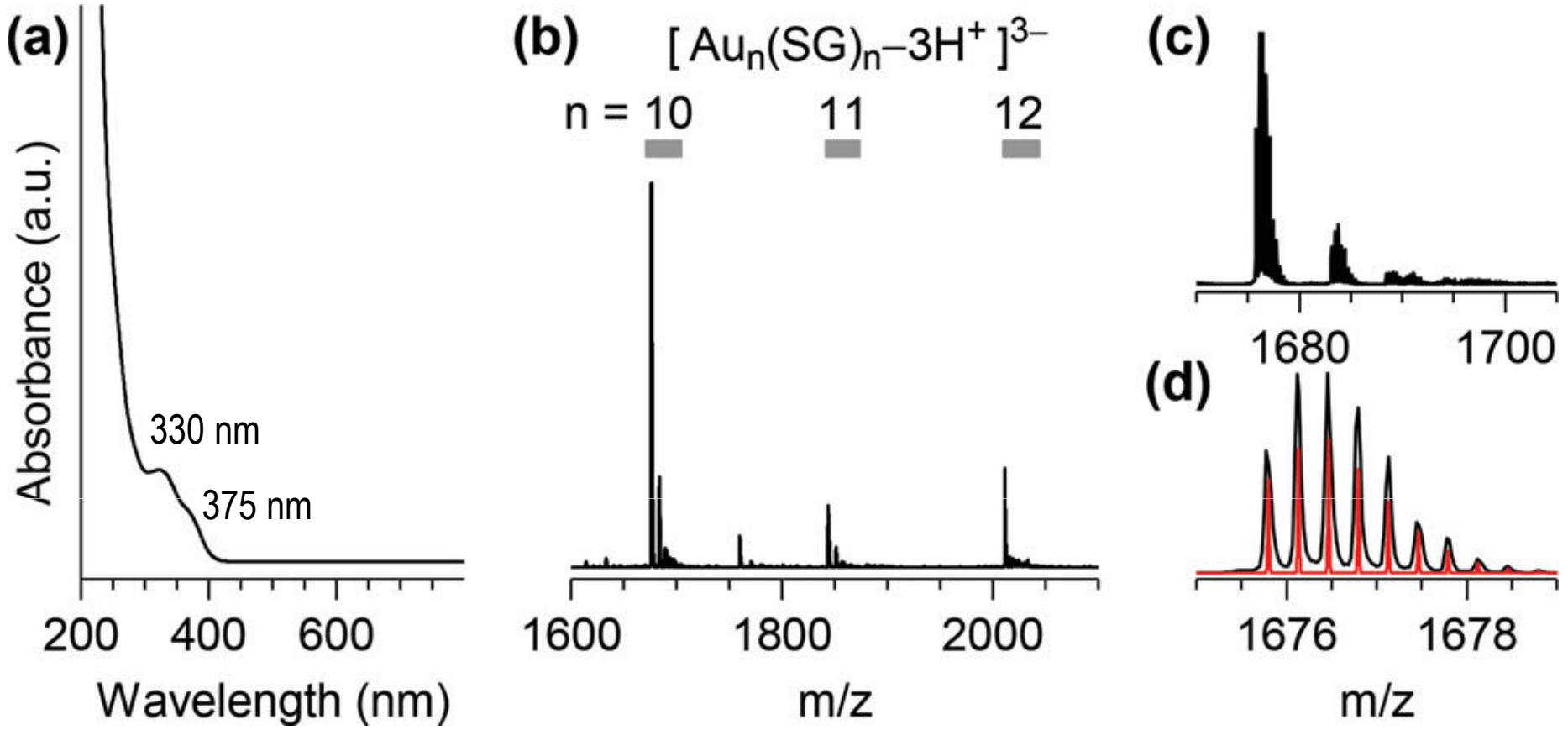
❑ No radiosensitizers in the current development can meet all these requirements.

In this work…

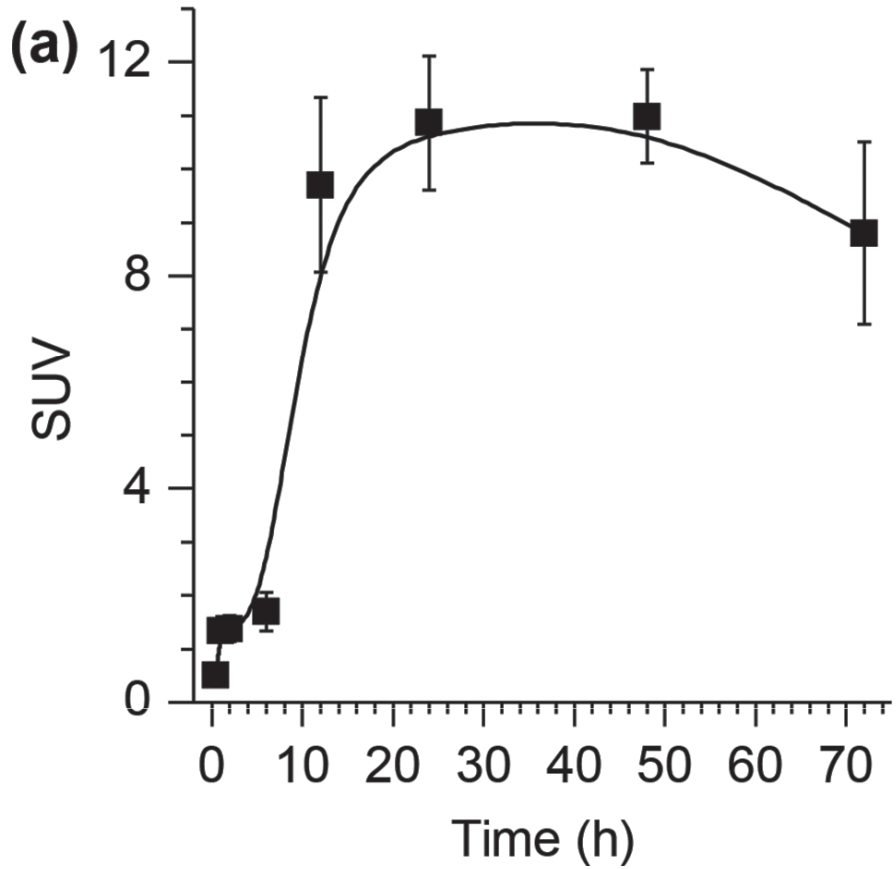
❑ A new class of radiosensitizer was prepared i.e. $Au_{10\text{-}12}$ $(SG)_{10\text{-}12}$ nanocluster which has high tumor uptake and targeting specificity.

Synthesis of $Au_{10-12}(SG)_{10-12}$ Nanocluster

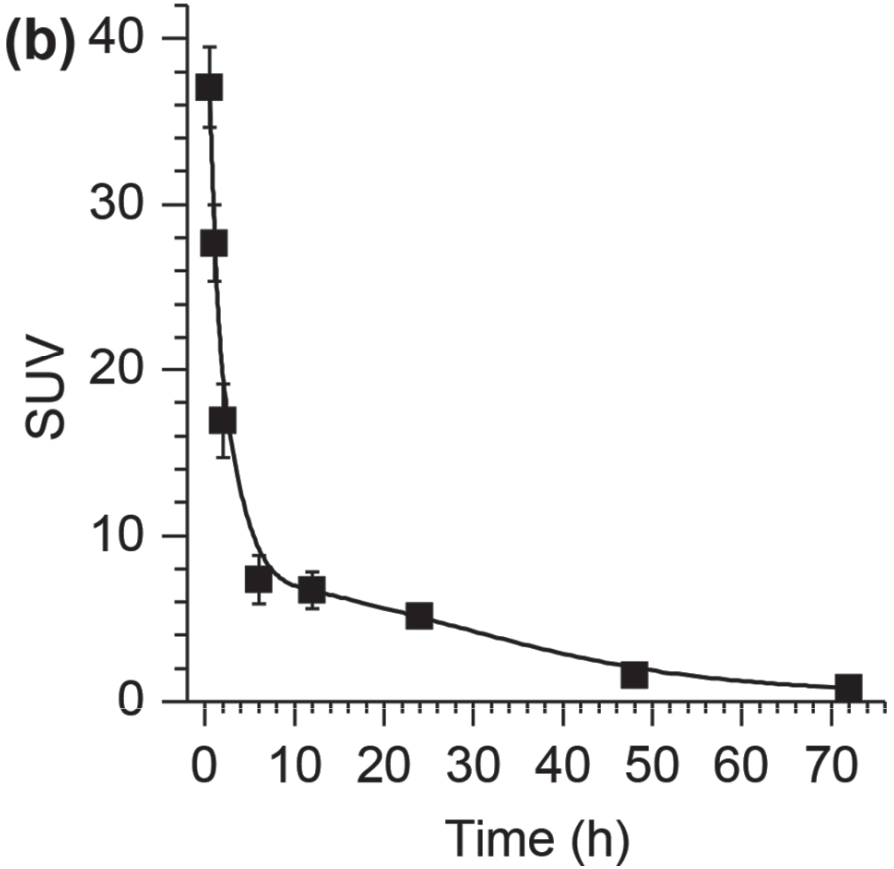




(a) UV-vis absorption and (b–d) ESI mass spectrum of the as-synthesized GSH-Au nanoclusters, indicating the formation of Au $_{10–12}$ (SG) $_{10–12}$ nanoclusters in the product. The series of isotope distributions shown in (c) are resulted from the replacement of the carboxyl H $^+$ of GSH by Na $^+$ or K $^+$. The red line in (d) is the simulated isotope distribution of [Au $_{10}$ (SG) $_{10}$ −3H +] $^{3–}$.

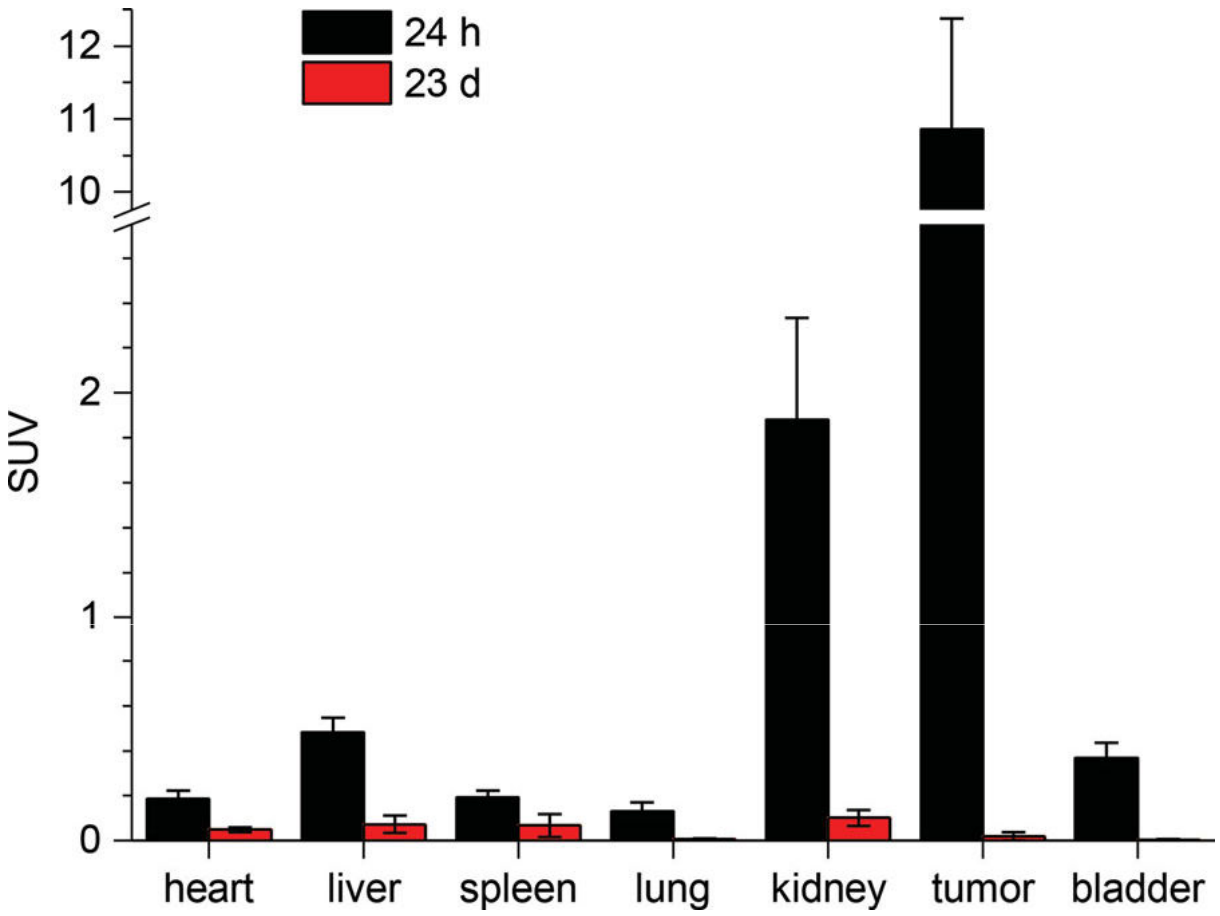


(a) Standard uptake values (SUV) of $Au_{10-12}(SG)_{10-12}$ Nanoclusters in tumor at different time points p.i.



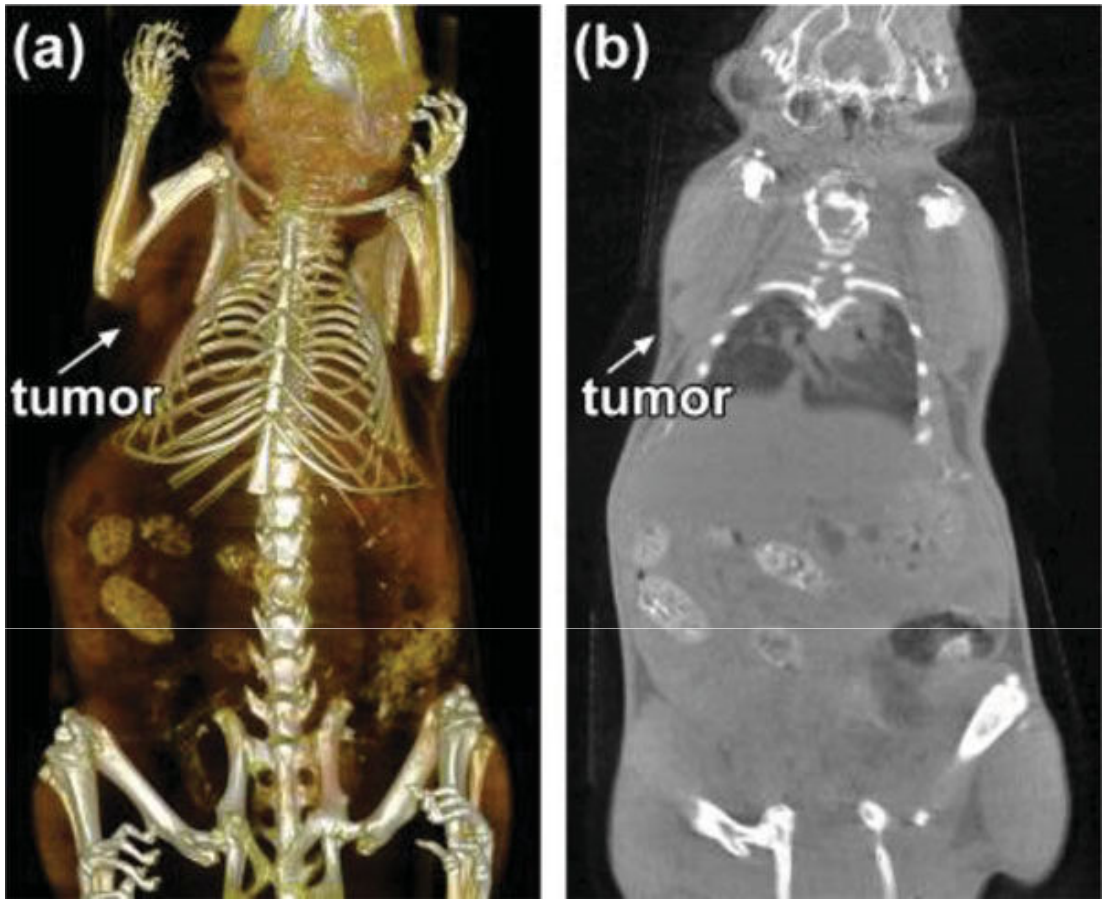
(b) Pharmacokinetics of $Au_{10-12}(SG)_{10-12}$ in mice from 0 to 72 h p.i.

It has distribution half life of ~ 2.4 h which is higher than $Au_{25}(SG)_{18}$ and other Au particles.
Clusters have blood elimination half life of ~ 22 h. Even after 24 h p.i., blood conc. of the clusters was still above 4.91 SUV. This value is ~ 20 times higher than that of reported small Au nps.



Biodistribution of Au $_{10-12}$(SG)$_{10-12}$ at 24 h and 23 days p.i.

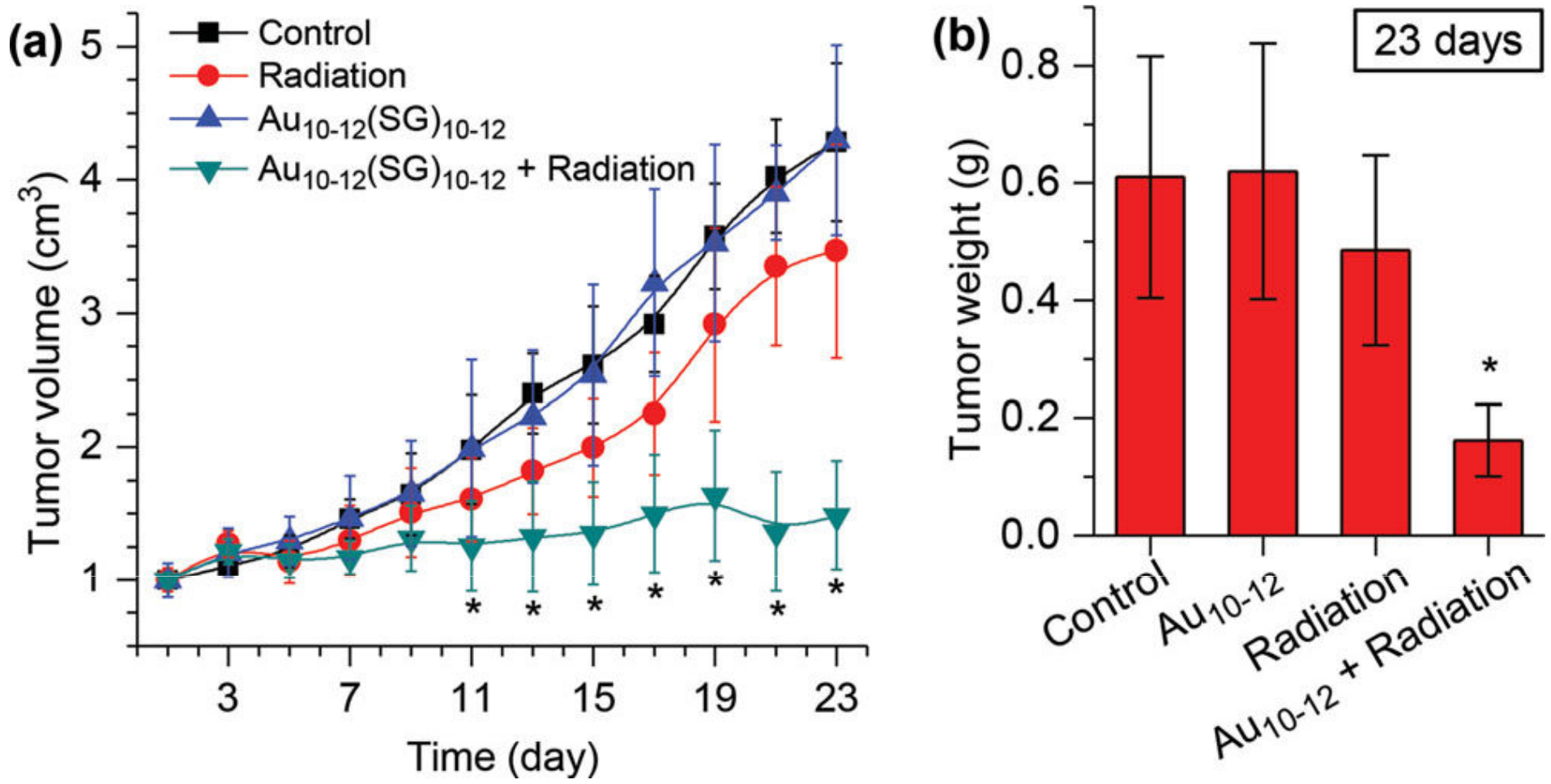
concentration of Au $_{10-12}$(SG)$_{10-12}$ nanoclusters in tumor was much higher than that of all other key organs including kidney and liver.
At 23 days p.i., the nanoclusters concentrations in all the key organs and the tumor were dropped below 0.019 SUV, which clearly suggest that Au $_{10-12}$(SG)$_{10-12}$ nanoclusters are highly renal clearable.



(a) Three- and (b) two-dimensional small animal X-ray CT imaging of $Au_{10-12}(SG)_{10-12}$ at 6 h p.i.

To confirm the selective deposition of Au clusters in tumor, X-ray computed tomography (CT) was used to image the distribution of the nanoclusters in body.

tumor uptake was clearly seen at the tumor site (indicated by arrows) at 6 h p.i. The corresponding CT value was determined to be 326 HU, which is significantly higher than that of the muscle tissue (207 HU).



a) Time-course studies of tumor volumes and (b) tumor weights (at 23 days p.i.) of untreated mice (control), mice treated with Au $_{10-12}$ (SG) $_{10-12}$ only, mice treated with radiation only, and mice treated with both Au $_{10-12}$ (SG) $_{10-12}$ and radiation. (*the star denotes significant difference from the control group)*

Summary

❑ The designed $Au_{10-12}(SG)_{10-12}$ nanoclusters showed efficient tumor uptake, high targeting specificity, and efficient renal clearance.

❑ As an attractive potential radiosensitizer, the toxicity response of $Au_{10-12}(SG)_{10-12}$ nanomolecules, including blood chemistry, biochemistry and pathology, were further examined. No Loss of the body weight or abnormal organ indices were observed

❑ No obvious damage to key organs including the liver, spleen, and kidney were observed in mice treated with $Au_{10-12}(SG)_{10-12}$ nanoclusters.

❑ The ultrahigh tumor uptake, targeting specifi city, and efficient renal clearance of ultrasmall $Au_{10-12}(SG)_{10-12}$ nanoclusters with highly exposed GSH ligands allows them to be ideal radiotherapy sensitizers that can enhance the safety and efficacy of radiotherapy.

SCIENTIFIC REPORTS

Ultrasmall Glutathione-Protected Gold Nanoclusters as Next Generation Radiotherapy Sensitizers with High Tumor Uptake and High Renal Clearance

Xiao-Dong Zhang[1], Zhentao Luo2, Jie Chen[1], Shasha Song[1], Xun Yuan[2], Xiu Shen[1], Hao Wang[1], Yuanming Sun[1], Kai Gao[3], Lianfeng Zhang[3], Saijun Fan[1], David Tai Leong[2], Meili Guo[4] & Jianping Xie[2]

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Thank you