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Use of Gold Nanostructures for Cancer Treatment

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Abstracts: ***Gold nanohexapods represent a novel class of optically tunable nanostructures consisting of an octahedral core and six arms grown on its vertices. By controlling the length of the arms, their localized surface plasmon resonance peaks could be tuned from the visible to the near-infrared region for deep penetration of light into soft tissues. Herein we compare the in vitro and in vivo capabilities of Au nanohexapods as photothermal transducers for theranostic applications by benchmarking against those of Au nanorods and nanocages. While all these Au nanostructures could absorb and convert near-infrared light into heat, Au nanohexapods exhibited the highest cellular uptake and the lowest cytotoxicity in vitro for both the as-prepared and PEGylated nanostructures. In vivo pharmacokinetic studies showed that the PEGylated Au nanohexapods had significant blood circulation and tumor accumulation in a mouse breast cancer model. Following photothermal treatment, substantial heat was produced in situ and the tumor metabolism was greatly reduced for all these Au nanostructures, as determined with ^{18}F-flourodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). Combined together, we can conclude that Au nanohexapods are promising candidates for cancer theranostics in terms of both photothermal destruction and contrast-enhanced diagnosis.***

Keywords: theranostics, gold nanostructures, near-infrared, photothermal effect, tumor ablation

1. Introduction

Photothermal treatment, also known as photothermal ablation or optical hyperthermia, has been actively explored as a minimally invasive approach to cancer therapy.[1] It is a procedure based on localized heating due to light absorption for selective destruction of abnormal cells. In general, near-infrared (NIR, 700–1100 nm) light is preferred for such an application as it can penetrate soft tissues deeply owing to the relatively low absorption/scattering by hemoglobin and water in this so-called transparent window.[2,3] The key component of this technique is a photothermal transducer that can absorb and convert NIR light into heat through a non-radiative mechanism with high efficiency.[4,5]

Over the past decade, many different types of photothermal transducers have been reported, including organic compounds or materials (*e.g.*, indocyanine green (ICG)[6] and polyaniline[7]), metal nanostructures (*e.g.*, Au nanostructures[8] and Pd nanoplates[9]), and carbon-based materials (*e.g.*, carbon nanotubes[10,11] and graphene oxide[12,13]). When combined with NIR light, all of them were able to generate sufficient heat to raise the local temperature and thus kill cancer cells. Of these photothermal transducers, Au nanostructures have received great interest in recent years due to the fact that their localized surface plasmon resonance (LSPR) peaks can be easily tuned to the NIR region by altering their size, shape, structure, or a combination of these parameters.[14] A wide variety of Au nanostructures, including aggregates of colloidal particles,[15]nanoshells,[16] nanocages,[17] nanorods,[18] and nanocrosses[19] have been demonstrated for photothermal cancer therapy with NIR light. In general, the nanostructures should have the following features: *i*) large absorption cross-sections in the NIR region; *ii*) easy functionalization with a "stealth" coating together with targeting ligands to maximize their accumulation at the tumor site following systemic administration; *iii*) appropriate size range (10–100 nm) to increase their blood half-life and to reduce removal by the reticuloendothelial system (RES); and *iv*) good biocompatibility especially in considering the possible long-term *in vivo* presence of the nanostructures.[20] Photothermal therapy has been demonstrated with certain types of Au nanostructures in early clinical trials. As an example, pilot clinical studies with AuroShell® (Au nanoshells with about 150 nm in diameter with a coating of polyethylene glycol 5000) have been approved by FDA and given intravenously to patients for the treatment of head and neck cancer, as well as primary and/or metastaic lung tumors.[21,22] However, developing Au nanostructures with all the aforementioned features remains to be achieved. For Au nanoshells, they are typically more than 100 nm in diameter and tended to be removed by the RES, primarily the liver and spleen.[22] As for Au nanorods, the cetyltrimethylammonium bromide (CTAB) used as a surfactant stabilizer for the synthesis could cause cytotoxicity and thus needs to be replaced prior to any *in vitro* or *in vivo* application.[23]

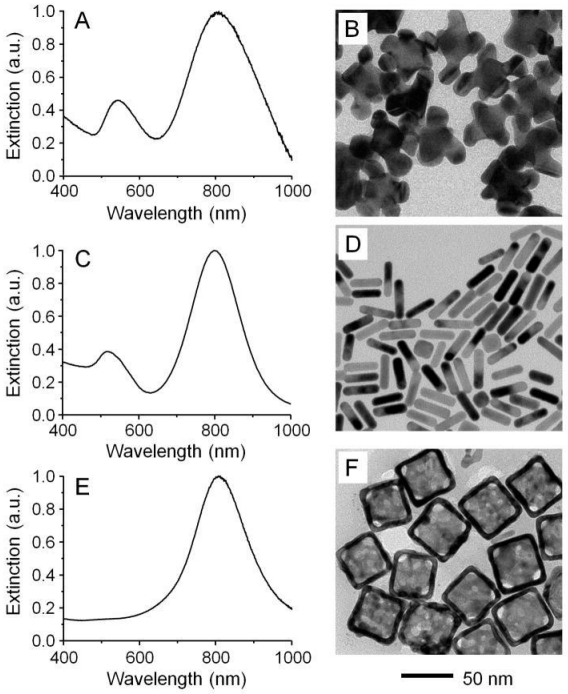
Branched or star-shaped Au nanostructures consisting of a core and protruding arms have recently received particular interest due to their unique morphology and optical properties.[24–27] Owing to the presence of sharp tips as well as their high surface-to-volume ratios, branched Au nanostructures could be more effective in photothermal conversion and drug loading relative to those with smooth surfaces.[27] We recently reported a new class of branched Au nanostructures -- Au nanohexapods, which consist of an octahedral core and six arms grown on its six vertices.[28] By controlling the length of the arms, the LSPR peaks of the Au nanohexapods could be easily tuned from the visible to the NIR region.[28] Therefore, Au nanohexapods are potential candidates as photothermal transducers for various theranostic applications.

Herein we assessed the potential use of Au nanohexapods as photothermal transducers by benchmarking against Au nanorods and nanocages. We found that Au nanohexapods exhibited a comparable photothermal efficiency, higher cell uptake, and lower cell cytotoxicity relative to Au nanorods and Au nanocages. More importantly, the *in vivo* photothermal treatment studies with a MDA-MB-435 breast cancer model showed that Au nanohexapods were also

effective for photothermal destruction of tumor, following either intravenous or intratumoral administration.

2. Preparation and Characterization of Au Nanostructures

The Au nanohexapods, consisting of an octahedral core and six arms grown on its six vertices, were prepared by reducing $HAuCl_4$ with DMF in an aqueous solution containing Au octahedral seeds using a previously published protocol.[28] By controlling the length of the arms, the longitudinal LSPR peak was tuned to 805 nm (Figure 1A) to overlap with the central wavelength of the diode laser (808 nm). In addition, a second peak was observed at 540 nm in the UV-vis spectrum, which could be attributed to the LSPR of the central octahedral core.[29] The surface of the as-prepared nanohexapods was covered by poly(vinyl pyrrolidone) (PVP, Mw ≈ 55,000), a biocompatible polymer. Figure 1B shows a typical TEM image of the nanohexapods, where the edge length of the octahedral cores was 25.3 ± 0.9 nm and the average dimensions of the arms were 16.3 ± 2.2 nm in length and 13.6 ± 1.8 nm in width, respectively. We measured the extinction coefficients of the Au nanohexapods by using inductively coupled plasma mass spectrometer (ICP-MS) analysis to quantitatively determine the concentration of Au nanohexapods in an aqueous suspension (see Supporting Information for how to calculate the volume of a Au nanohexapod), and then combined it with the extinction measured using a conventional UV-vis spectrometer to obtain a molar extinction coefficient of $5.5\times109\ M^{-1}\ cm^{-1}$ at the longitudinal LSPR peak position (805 nm). We then used a method based on photoacoustic (PA) imaging (λ=800 nm) to measure the molar absorption coefficient of the Au nanohexapods.[30] In this case, the PA signal intensities from suspensions of Au nanohexapods of various particle concentrations were plotted as a function of concentration. As shown in Figure S1, the PA signal increased linearly as the particle concentration was increased. The absorption coefficient of Au nanohexapods was then obtained by benchmarking the PA signal against a linear calibration curve obtained from a set of indocyanine green (ICG) solutions with different concentrations by using the molar absorption coefficient reported for ICG at λ=800 nm (Figure S2).[31] The molar absorption coefficient of the Au nanohexapods was found to be $5.0\times109\ M^{-1}\ cm^{-1}$, together with a ratio of absorption to extinction coefficients being 0.91. The large absorption cross section of Au nanohexapods indicated that these highly branched structures were effective in absorbing rather than scattering the incident light, suggesting their use as photothermal transducers for theranostic applications.



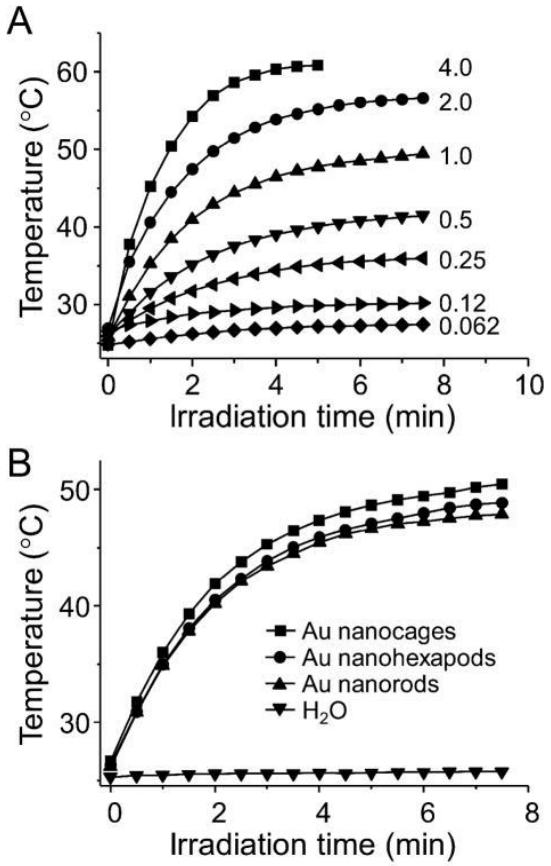
The widely investigated photothermal transducers, Au nanocages and Au nanorods, were chosen as benchmarks for a comparative study. Their LSPR peaks were also tuned to match the central wavelength of the laser diode (808 nm). The preparation of Au nanorods was performed using a seed-mediated growth method in the presence of the shape-directing surfactant CTAB as described in literature.[32, 33] The as-prepared Au nanorods had an LSPR peak at 800 nm (Figure 1C), and an average length and width of 36.2 ± 2.3 and 9.1 ± 1.7 nm, respectively (Figure 1D). Their surfaces were covered by CTAB. As for Au nanocages, they were prepared using a galvanic replacement reaction between Ag nanocubes and $HAuCl_4$according to our published protocol.[34] The as-prepared Au nanocages had an LSPR peak at 802 nm (Figure 1E), an outer edge length of 47.4 ± 4.5 nm and an inner edge length of 37.1 ± 2.7 nm, and a wall thickness of 5.2 nm (Figure 1F) and. Their surfaces were covered by PVP.

We also used the discrete dipole approximation (DDA) method to calculate the extinction cross section (σ_{ext}) of Au nanohexapods at various orientations and found several plasmon resonance peaks from 700 nm to 900 nm in addition to the resonance peak at 525 nm (Figure S3). The peak positions were in reasonable agreement with the experimentally measured values (Figure 1A). The appearance of only one relatively broad NIR peak in the measured UV-vis spectrum was likely caused by the random orientations of the particles in the solution and the polydispersity of the sample. Figure S3 also shows the scattering cross section (σ_{sca}) computed for a Au nanohexapod, and its absorption cross section ($\sigma_{ext,}$ data not shown) can be obtained from the equation: $\sigma_{ext} = \sigma_{abs} + \sigma_{sca}$. The ratio of σ_{abs} to σ_{ext} at 800 nm was calculated to be 0.96 for the Au nanohexapod, which was roughly on the same order as what (0.91) was obtained experimentally from PA and UV-vis measurements. It is worth noting that this ratio was larger than those calculated using DDA method for both Au nanocages (0.82) with an outer edge length of 45.0 nm

and Au nanorods (0.85) of 44.0 nm in length and 19.8 nm in width, but comparable to that (0.94) of Au nanocages with an outer edge length of 32.0 nm.[30]

Comparison of Photothermal Conversion *In Vitro*

We compared the photothermal conversion efficiencies of different types of Au nanostructures by measuring the temperature rise for their aqueous suspensions upon laser irradiation. Briefly, aqueous suspensions (100 μL) were placed in a single well of a 96-well plate and the radiation was delivered using a diode laser centered at 808 nm from the top at a density of 0.8 W/cm^2. A NIR camera was placed about 25 cm above the solution, and images were recorded at an interval of 15 s. The images were analyzed using the IR Flash software to obtain the average temperature of the suspension. As shown in Figure 2A, the suspension of Au nanohexapods (0.72 nM in particle concentration, with an extinction of 4.0 at 805 nm) showed a rapid increase in temperature during the first 3 min and eventually reached a plateau with a total temperature increase of 36.5 °C. The rate of temperature rise and the final temperature were proportional to the particle concentration; typically a slower and smaller increase was observed for a lower concentration of Au nanohexapods.



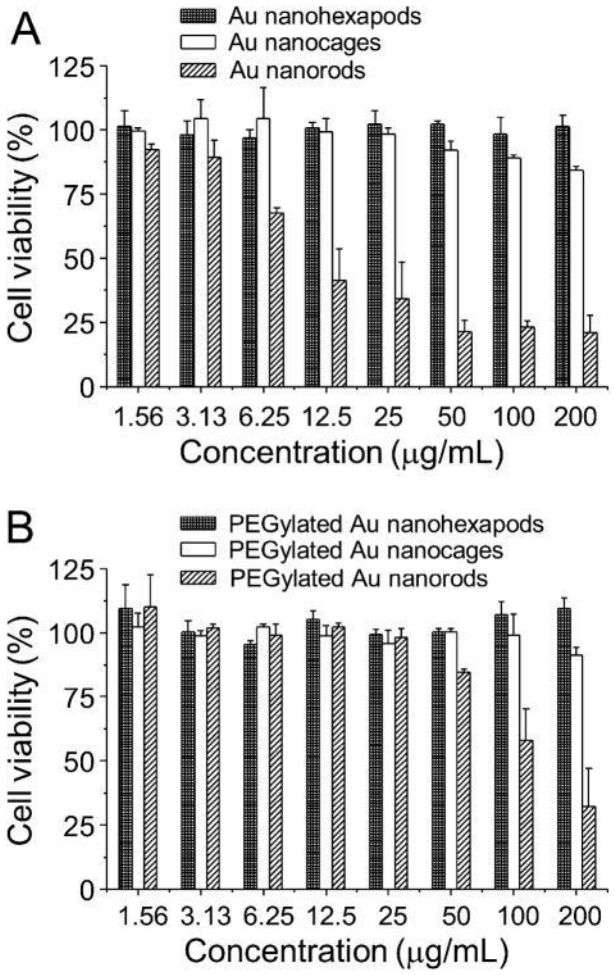
For the purpose of comparison, the extinction intensities of different samples were adjusted to 1.0 at 805 nm. As shown in Figure 2B, these three different types of Au nanostructures had a more or less similar efficiency for photothermal conversion on the basis of the same extinction intensity. However, given their large differences in structure and morphology, their conversion efficiencies could be drastically different when normalized to the total mass of Au atoms (or both Au and Ag atoms for the Au nanocage due to its alloyed composition).[35] As determined by ICP-MS, the concentrations of Au (or Au plus Ag for nanocages) atoms for the nanostructures were 34.4 μg/mL for nanohexapods, 36.4 μg/mL for nanorods, and 9.6 μg/mL for nanocages (together with an additional 3.3 μg/mL Ag atoms). As such, the photothermal conversion efficiency per Au atom was highest for nanocages, followed by nanohexapods, and then nanorods. It is worth noting that the continuous-wave diode laser caused no change to the optical properties of all three Au nanostructures, indicating that they were stable under the irradiation conditions. In the absence of any Au nanostructures, the solution only increased in temperature by 0.5 °C after 5 min of constant irradiation under similar conditions (Figure 2B).

3. Comparison of Photothermal Stability

We further characterized the photothermal stability of the Au nanostructures under pulsed laser irradiation. In a typical study, 100 μL of aqueous suspensions of Au nanostructures were exposed to a pulsed laser (λ = 805 nm) at a power density ranging from 15 – 35 mW/cm^2 for 15 min. The UV-vis spectra were taken to assess the stability. As shown in Figure S4, Au nanorods started to melt at 15 mW/cm^2, whereas Au nanohexapods and nanocages remained stable against laser irradiation under identical conditions without any observable LSPR shift. Both Au nanohexapods and nanocages started to melt at 25 mW/cm^2. Therefore, the Au nanohexapods and nanocages are much more photothermally stable than the Au nanorods.

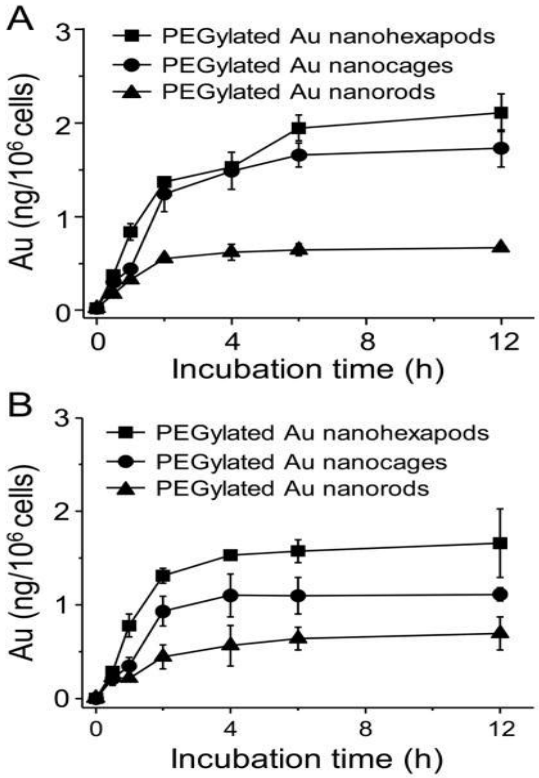
Cell Toxicity *In Vitro*

The toxicity of these Au nanostructures was assessed using an assay based on 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), which involves the use of mitochondrial functional activity as an indicator. Figure 3A shows cell viabilities of MDA-MB-435 breast cancer cells after incubation for 48 h with the as-prepared Au nanostructures at different concentrations ranging from 1.56 to 200 μg/mL of Au atoms. For the CTAB-coated Au nanorods, they displayed significant cytotoxicity at concentrations higher than 3 μg/mL, with a half maximal inhibitory concentration (IC_{50}) of 10 μg/mL, indicating that they were highly toxic due to the presence of CTAB. When the CTAB was replaced by PEG (Mw ≈ 5,000), the observed cytotoxicity disappeared for samples with roughly the same concentrations (Figure 3B), similar to what was observed by other groups.[23] For PVP-coated Au nanocages, they also showed observable cytotoxicity at high concentrations, with a 20% loss of cell viability at 200 μg/mL (Figure 3A). The toxicity of Au nanocages was most likely due to the presence of Ag atoms in the alloyed structure and subsequent release of Ag^+ ions from Au nanocages during incubation.[35] After coating with PEG, the toxicity of Au nanocages was also substantially reduced (Figure 3B). Importantly, no significant cell toxicity was observed for either as-prepared or PEGylated Au nanohexapods at all concentrations we tested. This could be attributed to their pure Au composition, as well as the absence of a toxic surface capping ligand.



Cell Uptake *In Vitro*

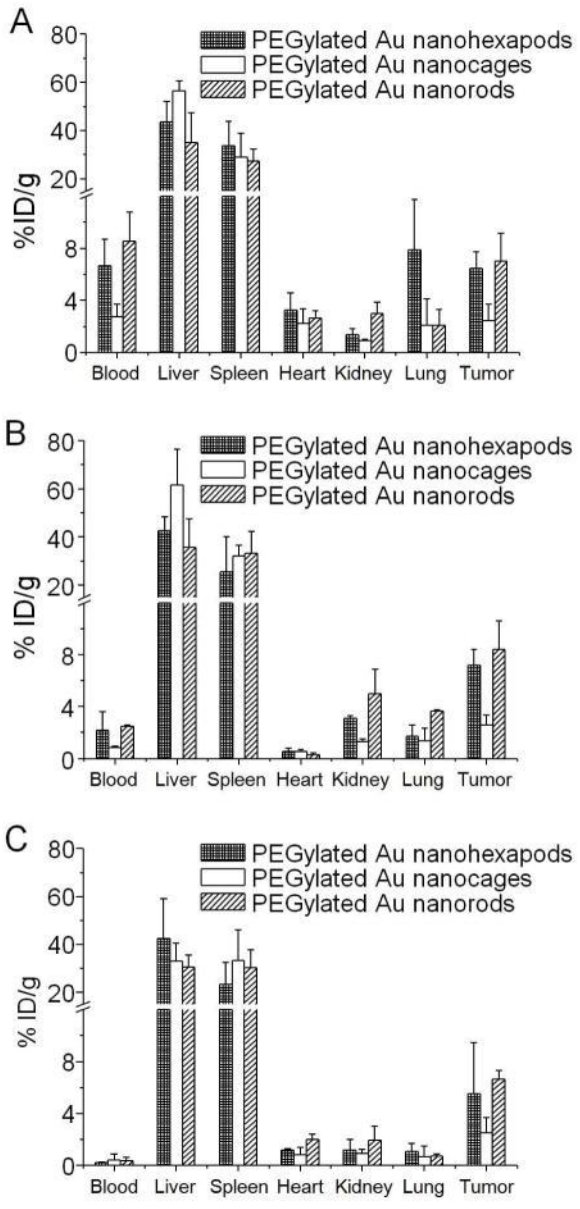
Efficient cell entry is a prerequisite for Au nanostructures to function as photothermal transducers or diagnostic agents. It is important to understand how the different geometries of these Au nanostructures will impact their uptake by cells. The cell uptake was assessed with MDA-MB-435 cells cultured on glass cover slips and placed either in the upright or inverted configuration (with the cells facing the bottom of the cell culture plate).[36] The intracellular Au content was measured using ICP-MS following incubation for different periods of time. It is known that different surface chemistries (*i.e.*, capping ligands) will lead to variation in nanostructure uptake.[37–39] Therefore, we used PEGylated Au nanostructures for the cell uptake study to eliminate such an effect. As shown in Figure 4A for the upright configuration, the cell uptake of Au nanostructures was dependent on their geometries. The uptake of PEGylated Au nanorods was lower than that of PEGylated Au nanohexapods, while PEGylated Au nanocages had an intermediate uptake value. At 12 h after incubation, the cell uptake of PEGylated Au nanohexapods by MDA-MB-435 cells was 3.2 and 1.2 times that of PEGylated Au nanorods and PEGylated Au nanocages, respectively. This result indicates that the branched morphology of Au nanohexapods might have a higher probability to enter the cell in comparison with the rod- or cube-like morphology. Similar trends were also observed for the inverted configuration, where the sedimentation factor was eliminated.[36] The cell uptake was generally lower for cells in the inverted configuration than in the upright configuration, especially for Au nanocages due to the relatively larger mass for individual particles as well as the lower surface-to-volume ratio. Cellular uptake of PEGylated Au nanohexapods was 3.0 and 1.5 times that of PEGylated Au nanorods and PEGylated Au nanocages, respectively (Figure 4B).



Biodistributions

We next used an *in vivo* tumor model based on the MDA-MB-435 cell line to compare the biodistributions of these PEGylated Au nanostructures in blood and tissues after intravenous administration and their passive targeting efficiencies. PEG has been widely used to prevent or minimize absorption of serum proteins from the blood and thus increase the blood circulation time of nanostructures. The tumors were generated through subcutaneous injection of MDA-MB-435 cells in the right flanks of athymic mice. After the tumors had reached a proper size, the PEGylated Au nanostructures (100 μL, 4 nM in particle concentration) were injected through the tail vein and the Au content contained in the blood and tissue samples were measured using ICP-MS at 6 h, 24 h, and 7 days post injection (p.i.). As shown in Figure 5 for the PEGylated Au nanohexapods, approximately 6.5±1.3 %ID/g (expressed relative to injected dose per gram tissue or blood) and 7.2±1.2 %ID/g of the injected particles were found in the tumor at 6 h and 24 h post-injection, respectively, suggesting significant accumulation in tumors due to the enhanced permeability and retention (EPR) effect in tumors with leaky vasculatures. The remaining PEGylated Au nanohexapods were taken up predominantly by the liver and to a lesser extent by the spleen related to the RES. Besides the liver and spleen, other organs with detectable Au levels were heart and lung, and to a less extent kidney. The mice injected with the PEGylated Au nanorods showed similar blood retention and accumulation (7.0±2.3 %ID/g at 6 h and 8.4±2.2 %ID/g at 24 h) in tumors. Both values were higher than the PEGylated Au nanocages (2.4±1.2 %ID/g at 6 h and 2.6±0.8

%ID/g at 24 h). On the other hand, different from PEGylatednanohexapods and nanocages, PEGylated Au nanorods showed a shift in distribution towards the spleen. At 7 days p.i., (Figure 5C), the levels of Au in the liver and spleen remained constant relative to those at 24 h. Interestingly, the concentrations of Au in the kidney and the blood pool organs (heart, lung, and blood) slightly decreased over time, indicating possible clearance of these Au nanostructures through the renal system. More importantly, the tumor accumulations of all these Au nanostructures did not show significant changes during the 7-day period of study, indicating stable residence in tumor. This feature might be advantageous for repeated or long term photothermal treatment. These results confirmed that the shape or morphology of nanostructures could influence their blood circulation and biodistributions. It should be pointed out that the dimensions of the Au nanostructures were different although the thicknesses of PEG coatings were roughly the same. Furthermore, our preliminary *in vivo* toxicity evaluation *via* hematoxylin and eosin staining did not show any observable adverse effect (Figure S5), indicating the *in vivo* biocompatibility of all these Au nanostructures.

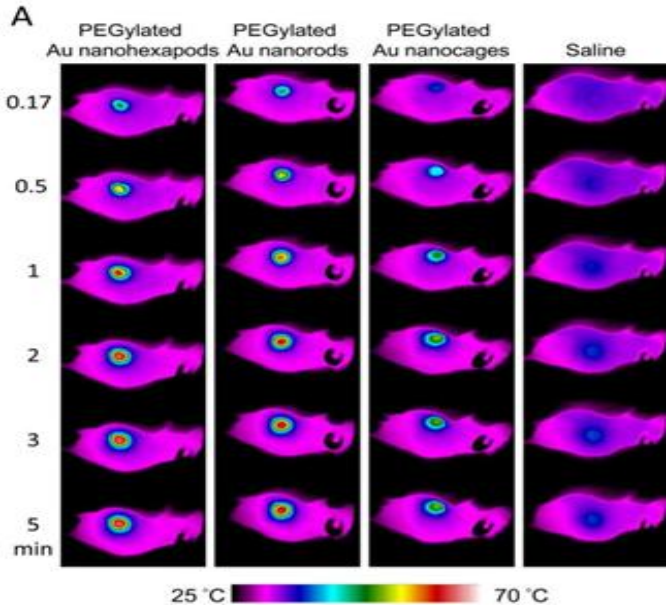


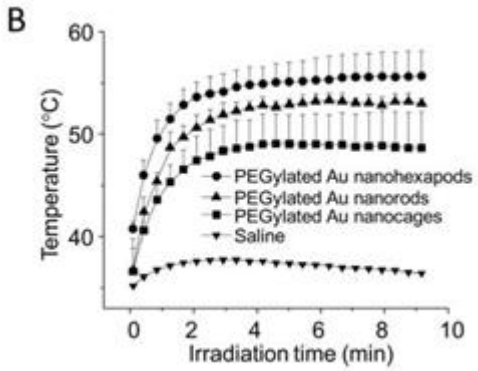
In Vivo Photothermal Capability of Au Nanohexapods

We first quantitatively analyzed the photothermal conversion of the Au nanohexapods using a tumor model. In a typical study, either 40 μL of 1 nM Au nanohexapods (Figure S6, A1–A4) or 40 μL of saline (Figure S6, B1–B4) was administered intratumorally to tumor-bearing mice. Immediately after injection, the tumor regions were irradiated with a diode laser (808 nm) at a power density of 1.0 W/cm^2 for up to 5 min. The spot size was adjusted to cover the entire tumor area. For the mouse injected with Au nanohexapods, thermal images recorded at different time points indicate that the temperature of the tumor region quickly increased and then reached a plateau upon laser irradiation. As shown in Figure S6C, the temperature could easily reach a level (ΔT = 23.1 °C) capable of inducing hyperthermia to kill cancer cells.[17] In comparison, for the control mouse injected with saline, the temperature recorded from the tumor region was still in the homeostatically tolerable region, with ΔT = 4.2 °C. This resultindicates that cell destruction will only result when Au hexapods and laser irradiation are both involved.

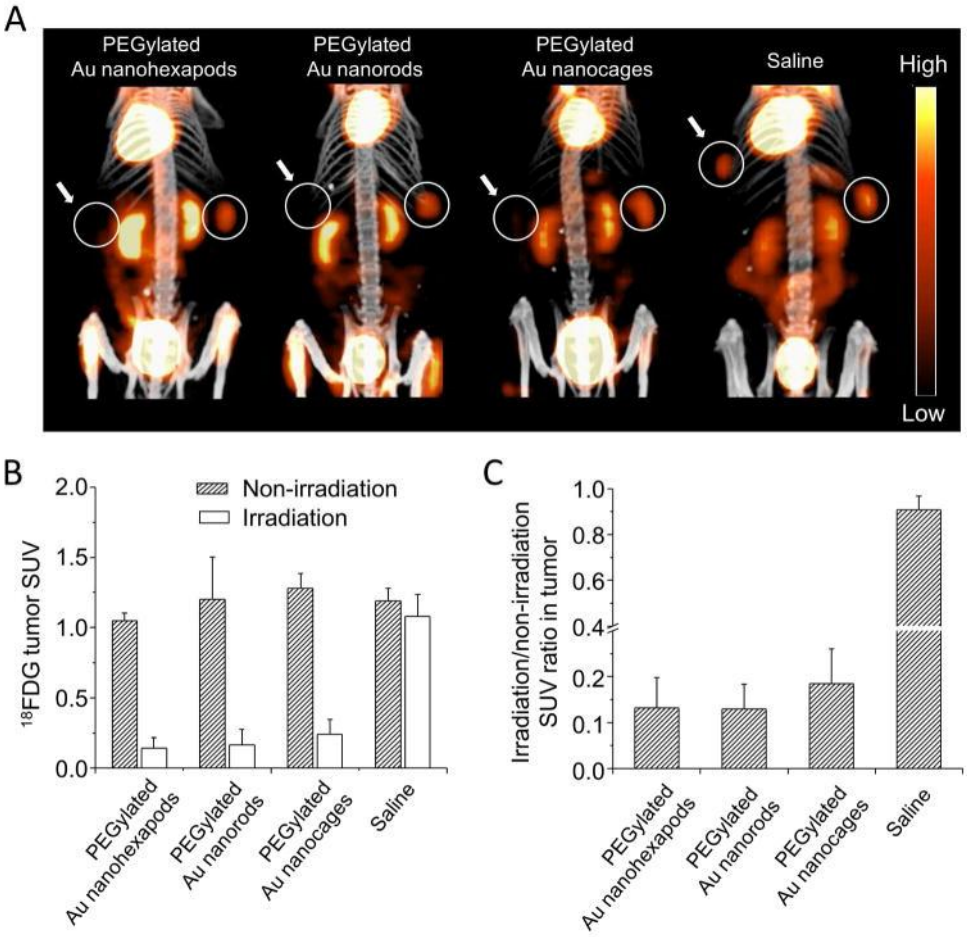
Comparison of Photothermal Treatment *In Vivo*

We further compared the photothermal cancer treatment efficacies of these PEGylated Au nanostructures in a bilateral MDA-MB-435 tumor model following intravenous administration. Tumor-bearing mice were administered intravenously with either 200 μL of the PEGylated Au nanostructures or 200 μL of saline, respectively (n = 3 per group). At 3 days post injection, the tumor on the left rear flank of each mouse was irradiated with a diode laser (808 nm) at a power density of 1.2 W/cm^2 for 10 min. For the mouse injected with PEGylated Au nanostructures, the temperature of the tumor region quickly increased and then reached a plateau upon laser irradiation, as compared with the mice injected with saline (Figure 6A). The images were analyzed using the IR Flash software to obtain the average temperature of the suspension (Figure 6B). When compared with the PEGylatednanorods (53.0±0.5 °C) and nanocages (48.7±3.5 °C), PEGylatednanohexapods showed the highest (55.7±2.4 °C) photothermal conversion efficiency *in vivo*, owing to their highest tumor uptake and photothermal conversion efficiency per Au atom.





We next evaluated the effects of photothermal treatment by observing the tumor metabolism with ^{18}F-FDG PET/CT. Following intravenous administration of the various types of PEGylated Au nanostructures or saline, ^{18}F-FDG PET/CT imaging was performed before and 24 h after laser treatment. As shown in Figure 7A, the ^{18}F-FDG uptake was significantly reduced in the irradiated tumors in contrast to the contralateral non-irradiated tumors. Quantitative analysis showed substantial decrease of tumor standardized uptake values (SUVs) after the treatment for all the Au nanostructures while the non-irradiated tumors showed constant metabolism during the study (Figure 7B). More importantly, the irradiation/non-irradiation tumor SUV ratios demonstrated approximately 90% reduction of tumor metabolism in mice treated with nanohexapods or nanorods and 80% decrease in mice treated with nanocages, indicating almost complete destruction of tumor glycolic activity after the photothermal treatment (Figure 7C). Further, four days after the treatment, no visible tumors were observed in any of the treated mice.



The results indicate that all these PEGylated Au nanostructures could serve as effective transducers for photothermal treatment of cancer. Although there was no significant difference in treatment response from photothermal therapy as determined by ^{18}F-FDG uptake among the three Au nanostructures under the experimental conditions used in the present work, nanohexapods did cause a higher rise in temperature than nanorods or nanocages. Taken together, it is reasonable to expect that the combined high photothermal efficiency, low cytotoxicity, and substantial accumulation in tumor make Au nanohexapods a candidate photothermal transducer for further *in vivo* therapeutic evaluation. However, there is still a long way to go before the nanohexapods and other types of Au nanostructures can be translated into clinical practice. More efforts need to be devoted to further improve the pharmacokinetics, targeting efficiency, and longitudinal toxicity.

4. Conclusions

In summary, we have evaluated the potential use of Au nanohexapods for applications in photothermal cancer treatment. Our comparison studies with Au nanohexapods, nanorods, and nanocages indicate that all these Au nanostructures could absorb and convert NIR light into heat. Au nanohexapods exhibited the highest cellular uptake and the lowest cytotoxicity *in vitro* for both the as-prepared and

PEGylated samples. The PEGylated Au nanohexapods also showed the significant blood circulation and tumor accumulation after intravenous injection. More importantly, the nanohexapods could significantly decrease the tumor metabolic activity following photothermal treatment after systemic administration. Combined together, it can be concluded that Au nanohexapods are promising as both optical therapeutic and diagnostic agents for a range of biomedical applications.

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