

Gold Nanocages and Their Biological Applications

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Gold has been one of the most mysterious metals ever since the very ancient times. In 1857, Faraday first reported that gold was pink when its size was extremely small.¹ This discrete optical property between metallic gold bars and particles was later attributed to surface plasmon resonance.² Driven by an incident electromagnetic wave, the free conduction electrons collectively resonate and selectively absorb incoming light of certain wavelength, which is the origin of those fascinating colors.

Interestingly, the SPR spectrum depends on the size, shape, and chemical composition of gold nanoparticles, as well as the external properties of the nanoparticles environment.^{3,4,5} This allows one to tune the SPR peaks of gold nanospecies. As to gold nanospheres, their SPR peaks can only be tuned between 510 nm to 650 nm with particle size varying from 8 nm to 150 nm.⁶ However, near-infrared light (800 - 1200 nm) is preferred in biomedical applications due to its deeper penetration (both blood and soft tissues are highly transparent within this range).⁷ Gold nanocages, a novel structure with hollow interiors and porous walls, have been studied to shift the SPR peaks to the near-infrared region.

The using of Ag nanocubes as a template for galvanic replacement with HAuCl_4 offers an elegant way to make complementary hollow gold nanocages with controllable void size, wall thickness, and wall porosity.^{8,9,10} With sharp-corner Ag nanocubes as a template, only gold nanocages with random pore sizes and locations are available. However, precise control over locations and sizes of pores can be achieved when using truncated Ag nanocubes as a template.¹⁰ Thanks to poly(vinyl pyrrolidone) (PVP) used during the synthesis of Ag nanocubes with truncated corners, only 111 face of Ag nanocubes are exposed to HAuCl_4 . Galvanic replacement thus starts and mostly takes place at these corners. Their SPR peaks can be conveniently and precisely tuned all the way from 400 to 1200 nm (Figure 1).

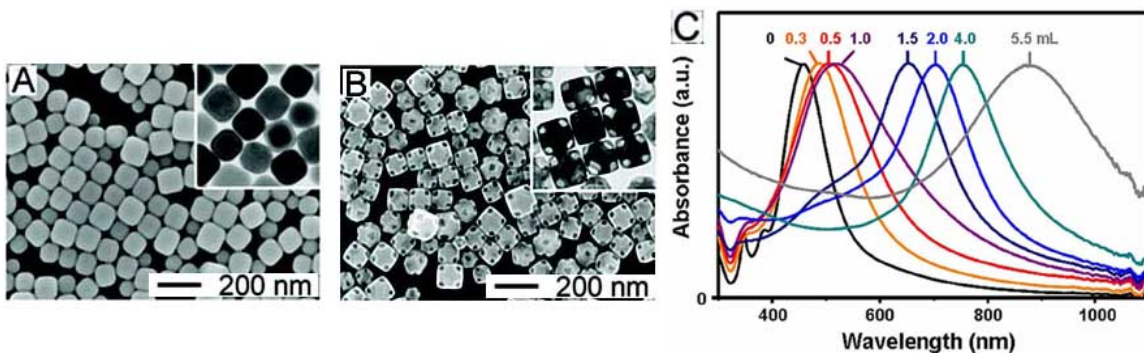


Figure 1: SEM and TEM (inset) of (A) Ag nanocubes with rounded corners and (B) Au nanocages. (C) Absorbance spectra of Au nanocages as products after reaction with 0, 0.3, 0.5, 1.0, 1.5, 2.0, 4.0 and 5.5 mL of 0.1 mM HAuCl_4 solution, respectively.

Both in-vitro and in-vivo studies have been accomplished to demonstrate their potential bio-medical applications.^{11,12,13} At the resonant frequency, most incident photons are absorbed by gold nanocages and converted into phonons or vibrations of the lattice thanks to their high absorption cross-section in NIR region. The subsequently generated heat can cause rise in temperature as well as thermo-elastic expansion, which can be applied in bio-imaging and photothermal therapy respectively. Due to their hollow interiors and porous walls, gold nanocages might also be used as a drug delivery system. Like other gold nanospecies, the surface of gold nanocages could be readily functionalized with bio-molecules or polymers via gold-thiol chemistry to improve the biocompatibility without shifting the SPR peaks significantly.^{11,12}

Kim *et al.*¹¹ has applied gold nanocages as a contrast agent for photoacoustic (PA) tomography on B16 melanomas in vivo. The gold nanocages studied in this project have an outer edge length of 46 nm and a wall thickness of 7 nm, with the surface functionalized by hormone or poly(ethylene glycol). Bioconjugated gold nanocages (MSH-AuNCs) show specific targeting towards tumor cells, thus higher cellular uptake and stronger contrast enhancement compared with the control (PEG-AuNCs). The background vasculature images are obtained by photoacoustic microscope at 570 nm while the melanomas images are recorded with 778 nm in a time course.

Chen *et al.*¹² has applied gold nanocages as photothermal therapy against the U87MGwtEGFR human glioblastoma cell line in mice. The gold nanocages studied in this project have an outer edge length of 48 nm and a wall thickness of 3.5 nm, with PEG attached to the surface. For the nanocage-injected mice, the rapid increase of temperature to 50 °C on the tumor surface is observed within one minute, which is in sharp contrast to saline-injected mice. ¹⁸F-FDG PET/CT co-imaging technique is employed to monitor the treatment response and confirm the decreased metabolic activity in tumors after the photothermal therapy.

Yavuz *et al.*¹³ has proved the concept that gold nanocages could be applied in triggered release with NIR light. The gold nanocages studied in this project have an outer edge length of 50 nm, a wall thickness of 3.5 nm, and a pore size of 5-10 nm. The out surface is coated with a thin layer of temperature-sensitive polymer, poly(NIPAm-co-Am). The collapse and stretching of the polymer coatings can be controlled by laser on and off, leaving the pores of nanocages exposed and covered respectively. The subsequent controlled release of the pre-loadings has been demonstrated with dyes, drugs, and enzymes.

In summary, due to their tunable SPR peaks, simple synthetic method and hollow-porous structure, gold nanocages represent a new class of nanoscale agents for applications in bio-imaging, photothermal therapy and controlled release. Hopefully, the synergetic effect of these three applications might provide better anti-cancer effect. However, serious issues like toxicity¹⁴ and stability¹⁵ need to be addressed comprehensively before any real applications.

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