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GOLD NANOCAGES: AN EXCELLENT MEDICAL CONTROL

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Abstract

A nanocage is a hollow nanoparticle. Noble-metal (such as gold, silver, platinum, etc.) nanocages comprise a novel class of nanostructures possessing hollow interiors and porous walls. The applications of these nanocages have been reported widely, owing to their unique and tunable optical, electronic, and catalytic properties. The manipulation of matter at the atomic and molecular scale leads to significant changes both in physical and chemical properties of matter, thus making such nanocages unique. Gold (Au) nanostructured materials provide a promising platform for early cancer detection and treatment. As the Au nanocages have large absorption cross-sections, they act as effective photothermal transducers, which when targeted to cancer cells could provide a therapeutic effect by selectively killing them by hyperthermia. Because of many merits such as a high degree of size and shape control, easily functionalized surface, and low cytotoxicity, Au nanocages have proven to be a versatile and multifaceted platform for a variety of applications in nanomedicine such as photo-thermal cancer treatment, controlled drug release, photon luminescence imaging, photo-acoustic tomography /***

Keywords: Gold nanocages, Nanomedicine, Photo-thermal cancer treatment, Controlled drug release, Photon luminescence imaging, Photo-acoustic tomography

1. INTRODUCTION

Gold-based nanocages are hollow, porous structures with dimensions < 100 nm. While gold nanoparticles absorb light in the visible spectrum of light (at about 550 nm), gold nanocages absorb light in the near-infrared, where biological tissues absorb the least light. New properties emerge when the size of a matter is reduced from bulk to the nanometer scale. These new properties, including optical, magnetic, electronic, and structural properties, make nano-sized particles very promising for a wide range of biomedical applications such as cellular imaging, molecular diagnosis and targeted therapy depending on the structure, composite and shape of the nanomaterial. When a Au nanostructure is illuminated with electromagnetic wave of an appropriate wavelength, its conduction electrons will be driven by the electric field to collectively oscillate relative to the lattice of positive nuclei, creating intense extinction peaks (extinction = absorption + scattering) at resonant wavelengths. Most of the gold nanaocage applications in medicine are based on this optical phenomenon known as localized surface plasmon resonance (LSPR)[1].

2. TWO- & THREE-PHOTON LUMINESCENCE IMAGING

When the size of metal nanoparticles is under sub-wavelength, free electrons in the nanoparticles oscillate collectively. The surface plasmon excitation then can result in enhancements of absorption, scattering, and local electric field. To be specific, for biomedical imaging, the LSPR of nanoparticles can enhance the optical signal characteristics of certain organizations so as to improve the contrast of imaging which has important application in early cancer detection and diagnosis. Gold nanostructures can be optically excited to emit luminescence through a recombination of excited electrons in the sp- conduction band with holes in the d-band, and this capability can be used for cellular imaging. This luminescence is significantly enhanced when the LSPR peak of Au nanostructures, such as Au nanocages, matches with the wavelength of the photons used to excite the electrons (typically a near infrared region (NIR) laser). Two photon luminescence (2 PL) imaging provides a simple and effective means to examine and quantify the cellular uptakes of Au nanocages[1].

However, the heat generated from Au nanocages, owing to the overlap between the LSPR peak of Au nanocages and excitation laser in 2 PL, may cause adverse effects on the biological sample. In comparison, the absorbed photons are more effectively used for the generation of luminescence rather than heat in the case of three-photon luminescence (3 PL). Figure 1

compares the efficiency and photothermal toxicity of 2 PL and 3 PL for imaging Au nanocages in living cells and tissues. Two KB (tumour) cells with similar density of Au nanocages were illuminated by a 760 nm laser at 1.9 mW for 2 PL imaging and a 1290 nm laser at 4.0 mW for 3 PL imaging. As shown in Fig. 1a) and (d), Au nanocages in cells could be visualized by both 2 PL and 3 PL with a similar level of intensity. After 90 seconds scanning with 760 nm laser, membrane blobbing occurred as indicated by ethidium bromide staining (shown in green), together with reduced luminescence intensity from Au nanocages [Fig. 1(b)]. In contrast, neither damages to the plasma membrane nor reduction of luminescence intensity was observed during 90 second 3 PL imaging [Fig. 1(e)]. Another advantage of 3 PL imaging is the complete suppression of auto-fluorescence from the tissue at 1290 nm excitation, making the 3 PL signal from Au nanocages much easier to be resolved. Figure 1(c) and (f) compares the 2 PL and 3 PL micrographs taken from the same liver tissue slice containing Au nanocages. Clearly, 2 PL imaging caused a much stronger background than 3 PL imaging, primarily due to auto-fluorescence from the tissue.

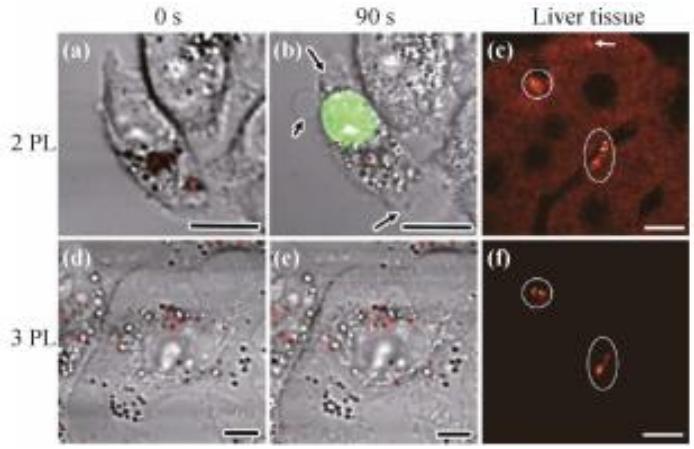


Fig 1: Comparison of two- and three-photon luminescence (2PL and 3PL) imaging of Au nanocages in (a, b, d, e) KB cells and (e, f) liver tissues.

3. PHOTOACOUSTIC TOMOGRAPHY

Photoacoustic tomography (PAT) is a powerful hybrid biomedical imaging modality that offers both strong optical absorption contrast and high ultrasonic resolution. When tissue is irradiated with a pulsed laser source, the resulting heat creates an acoustic signal that can be detected and converted into an image by a scanning transducer. Significantly, the signal can be enhanced using contrast agents that strongly absorb light, such as Au nanostructures.

The use of Au nanocages as intravascular contrast agents for PAT imaging of cerebral cortex in rat model and sentinel lymph nodes have been demonstrated. A recent study, demonstrated that the use of [Nle4, D-Phe7]-α-melanocyte stimulating hormone (a melanoma specific peptide) conjugated Au nanocages, Fig. 2(a) as a novel contrast agent for in vivo molecular PAT imaging of melanomas with both exquisite sensitivity and high specificity. Figure 2(b) shows an experimental setup of the PAT system, where 10 MHz macroscopic and 50 MHz microscopic dark-field PAT systems were used to image the melanoma and its surrounding micro-vasculatures, respectively.

The average PA signal (golden color) within the melanoma at 6 h post-injection increased by up to 36%. It is worth pointing out that the [Nle4, DPhe7]-α-MSH-Au nanocages enhanced contrast ~300% more than poly ethylene glycol (PEG), as confirmed by the inductively-coupled plasma mass spectrometry (ICP-MS) data. This observation indicates that Au nanocages can be effectively delivered to a tumour target by modifying their surface with a ligand that specifically binds to a biomarker over expressed on the tumour surface[2].

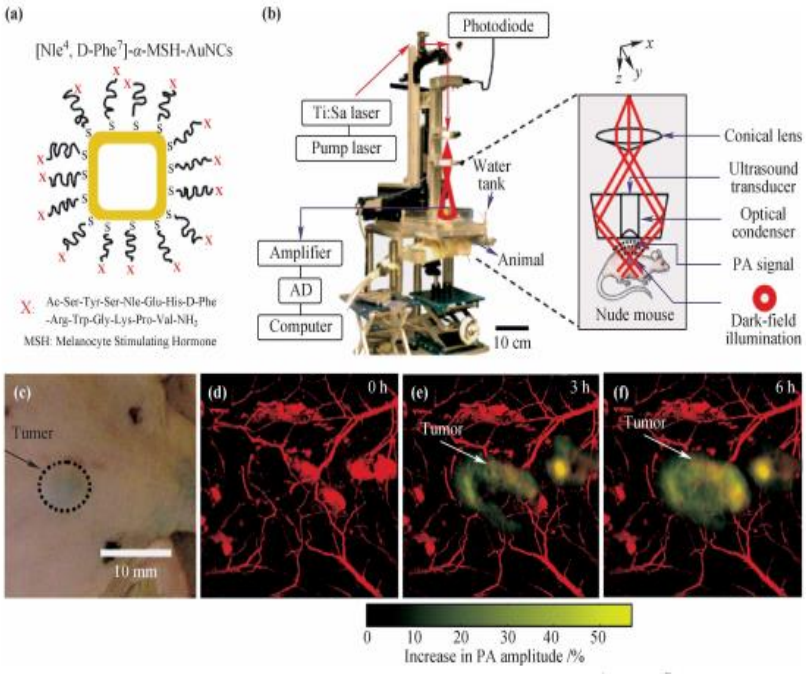


Fig 2: In vivo molecular photoacoustic tomography (PAT) of melanomas using [Nle4, D-Phe7]-α-MSH conjugated Au nanocages as contrast agents.

4. PHOTOTHERMAL CANCER TREATMENT

Gold nanostructures with localized surface polasmon resonance (LSPR) peak in the near infrared region region are particularly attractive for cancer treatment based on the photothermal effect. In the transparent window from 700-900 nm, the incident light can penetrate deeply into soft tissues, ensuring high efficacy for cancer treatment with minimum side effects. The key component of this approach is a photothermal transducer capable of absorbing NIR light with a large cross section and then converting the light into heat with high efficiency. Gold nanocages with tunable LSPR peaks in the NIR region are particularly suitable for the use as photothermal transducers, whose NIR absorption cross section can be five orders of magnitude greater than the conventional organic dyes such as indocyanine green. [3]

Experimentally, tumour-bearing mice were intravenously injected with either 100 µL of saline or 100 µL of PEGylated Au nanocages. After 72 h post-injection, the tumour on the right flank of each mouse was subjected to photothermal treatment by exposure to a continuous wave diode laser at 808 nm at a power density of 0.7 W/cm2 for 10 min. As monitored by an infrared camera, the tumour containing Au nanocages was rapidly heated to 50 ◦C within 1 min and then to a plateau temperature at 55◦C after 2 min while essentially no change was observed for saline.

To evaluate the treatment response, 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) was used to monitor the changes in metabolic activity before and after photothermal therapy. Before laser irradiation, 18F-FDG uptake showed no significant difference between saline-injected mice [Fig. 3(a)] and Au nanocages-injected mice [Fig. 3(b)]. At 24 h post-laser treatment, 18F-FDG uptake in tumours of Au nanocages-injected mice [Fig. 3(d)] was significantly reduced as compared to that of saline-injected mice [Fig. 3(c)].

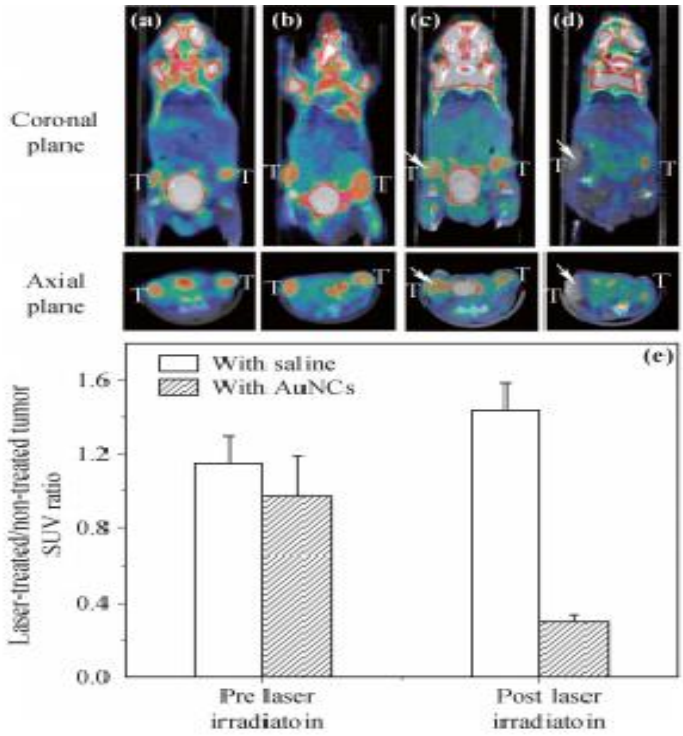


Fig 3: Gold nanocages for photothermal cancer treatment. A saline-injected mouse (a) prior to and (c) after laser irradiation; An Au nanocages-injected mouse (b) prior to and (d) after laser irradiation. (e) plot showing the ratios of laser-treated tumour to non-treated tumour

5. CONTROLLED DRUG RELEASE

By taking advantage of their hollow interiors and photothermal effect, Au nanocages have been used as a novel class of drug delivery vehicles. This feature is particularly attractive for nanomedicine because Au nanocages can be monitored with optical imaging techniques while a drug is released at the targeted site[3].

A controlled drug release system can be created by filling the hollow interiors of Au nanocages with a drug-doped phase-change material (PCM) such as 1- tetradecanol which has a melting point of 38–39 ◦C. PCMs with a surfactant-like structure, such as those containing both long hydrophobic tails and hydrophilic heads, are preferred to ensure good miscibility with drug molecules. As long as the drug is miscible with the PCM, it can be easily loaded into the Au nanocages via the diffusion of PCM-drug mixture.

Since the physical state of a PCM can be reversely changed over a narrow temperature range, it can confine the preloaded drug molecules inside the Au nanocages until it is heated to a

temperature beyond its melting point, resulting in the release of drug through diffusion [Fig. 4(a)]. As shown in Fig. 4(b), the release can be readily controlled by varying the power of high-intensity focused ultrasound (HIFU) or the duration of exposure to HIFU[4].

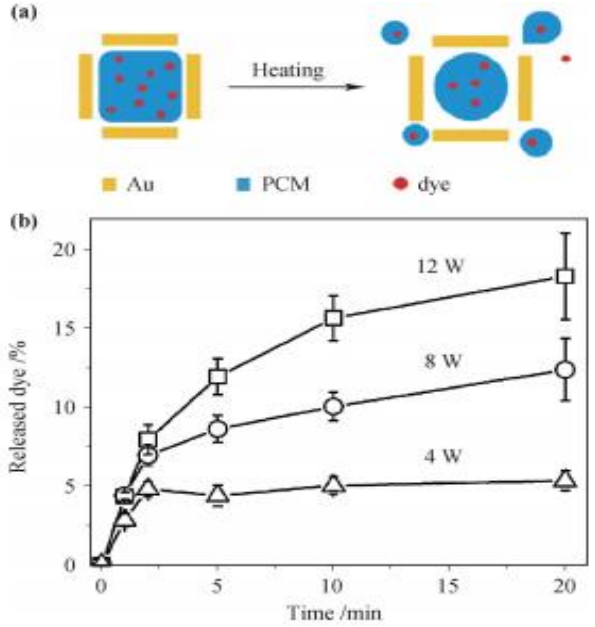


Fig 4: Gold nanocages as delivery vehicles for controlled drug release. (a) Schematic illustration of the loading and then release of a dye from an Au nanocage through the assistance of a phase change material (PCM). (b) Release profiles of the dye exposed to HIFU at different applied powers and time points.

6. CONCLUSIONS

Owing to their relative bio-inertness, ability to be surface modified, and tunable LSPR, Au nanocages represent a new class of nanoscale agents for applications involving cancer diagnosis and treatment. Great progress has been made in this field in recent years: they can be used as optical tracers or contrast agents for various imaging and diagnostic modalities; they can kill cancer cells through the photothermal effect; they can be used to load and release drugs in a controlled manner. The unique features of Au nanocages will likely make them a platform nanomaterial for a range of applications in nano-medicine.

Work is underway to expand the *in vivo* applications of the Au nanocages. The greatest challenge now is to enhance our understanding of the behaviours and fate of Au nanocages in complex in vivo environments, and further extend their capability to clinical use.

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