# Metal Nanoshell – Capsule for Light-Driven Release of a Small Molecule

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We report the release of small molecules from the metal nanoshells driven by laser irradiation. The metal nanoshells were composed of 50 nm silica cores and variable thickness silver shells of 10 and 30 nm. The small-molecule fluorophores of Rhodamine 123 were physically absorbed in the silica cores of metal nanoshells and released through the metal walls. The release rate was significantly increased with the laser irradiation depending on the metal shell thickness; a thicker metal nanoshell led to a faster release. The results were interpreted by the photothermal effect of metal nanoshells that could convert the light into thermal energy via coupling interactions of light with the metal plasmon resonances of shells. The metal nanoshells may be potentially used as capsules for the controlled release of drugs as other molecules.

### Introduction

Chemotherapeutic modalities have significant side effects, including high costs and poor clinical outcomes.<sup>1</sup> The controlled release approach thus is attractive in research and treatment.<sup>2</sup> Generally, the controlled release of small-molecule drugs is realized by loading the drugs in the capsules followed by passive release. Such a strategy can significantly reduce the side effects and improve the outcomes in the therapy. A number of drug carriers have been developed, for example, nanoparticles, liposomes, polymers, and so forth.<sup>3,4</sup> Regardless of the kind of carrier employed, the small-molecule drugs are released by diffusion through the walls of the capsules.<sup>5</sup> The release can be described by two approaches, temporal and distribution. However, both processes have obvious drawbacks in the release events. In the temporal control, the drugs are released over an extended duration or at a specific time and can be rapidly metabolized and/or eliminated from the body after administration. As the result, the drug concentration may fluctuate widely after the drugs are administered via bolus injection, and only a portion is in the therapeutic window. In the distribution control, a portion of the drug is released before the capsules come to the target sites in the body. Consequently, the drugs in the carriers cannot completely take effect in the therapies. Therefore, it is of importance to develop a novel strategy that can control the drug release precisely with both time and location specifics.

Metal nanoparticles can convert light into thermal energy under laser irradiation,<sup>6–10</sup> which results in couplings of the irradiation light with the plasmon resonances from the metal nanoparticles.<sup>11</sup> Such an energy conversion may lead to a rise in local temperature and an increase in the small-molecule diffusion rate through the capsule walls. Skirtach and colleagues have reported conjugation of the metal nanoparticles on the polymer reservoirs to investigate the light-driven release of small-molecule fluorophores.<sup>12,13</sup> The results showed that without light irradiation, the release was almost blocked, whereas with light irradiation, the release was increased significantly. Thus, we believe that the metal-nanoparticle-associated capsules can be used for the time- and location-specific release of small molecules. In this paper, a new type of capsule with metal association, the metal nanoshell, is reported. Compared with the individual metal nanoparticles, the metal nanoshells are known to display more intense plasmon resonances due to greater metal amount as well as dense metal structures.<sup>14,15</sup> Thus, efficiency in light-thermal energy conversion by the metal nanoshell is expected to be higher in a broadened region. In addition, the plasmon resonances of metal nanoshells can be wider from the visible to near-infrared region, depending on the thicknesses of the metal shells and the diameters of the cores.<sup>14–16</sup> It is known that the tissues and water have little absorbance in the near-infrared region; therefore, the light at the near-infrared region can transmit through the skin to the target sites in the body. The metal nanoshells can be bound with the probes of biological interest via versatile surface chemistry, so that they can be target-specifically conjugated in the body.<sup>16</sup>

Photothermal effects by the metal nanoshells can be applied in therapeutic treatments. Halas and colleagues have observed tumor thermotherapy without drugs when metal nanoshells were location-specifically conjugated with the tumor targets and irradiated with a laser beam at a near-infrared wavelength.<sup>19,20</sup> When the metal nanoshells are loaded with the small-molecule drugs and the loaded drugs are released in a light-irradiationcontrolled approach, with the combination effects of photo- and chemotherapy, the efficiency may be improved significantly. When the metal nanoshells are used as the capsules to load with the small-molecule drugs, the release thus can be controlled in the location. Our recent research has demonstrated that the metal nanoshells can load the small molecules in the cores.<sup>17,18</sup> Thus, the study to the both time- and location-specific controlled release of small molecules from the metal nanoshells with light irradiation is an attractive method.

In this research, we loaded the small molecules in the metal nanoshell capsules and studied the controlled release of loaded

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small molecules. The metal nanoshells were synthesized with the silica cores and silver shells. We were concerned with the photophysical behaviors of these metal nanoshells as the capsulates in the controlled release of small molecules. In the strategy described by Skirtach, the small-molecule fluorophores were used as the probes for research convenience.<sup>12,13</sup> These small-molecule fluorophores were loaded in the metal nanoshells and then irradiated with a laser beam. The release of the fluorophore from the metal nanoshell was monitored by the concentration of released fluorophore in solution.

### Materials and Methods

All reagents including Rhodamine 123 and spectroscopicgrade solvents were used as received from Sigma-Aldrich. Nanopure water (>18.0 M $\Omega$ .cm) was purified using a Millipore Milli-Q gradient system for all experiments.

**Preparation of the Metal Nanoshell.** The silica spheres were prepared by a modified Stöber method.<sup>21</sup> Typically, 1.5 mL of tetraethyl orthosilicate was dissolved in 50 mL of ethanol and then 2.0 mL of 30% ammonia was added under vigorous stirring. The mixture was stirred at room temperature overnight. The suspension was removed by centrifugation. The residual was washed thoroughly with ethanol and redispersed in 50 mL of ethanol, and 10  $\mu$ L of 3-aminopropyltrimethoxysilane was added in aqueous solution. The solution was continuously stirred for 2 h at room temperature for surface amination on the silica spheres. These aminated silica spheres were recovered by centrifugation, washed with ethanol, and dispersed in 100 mL of water.

To deposit the silver nanoshells, we first bound the small silver nanoparticles as the seeds on the silica spheres. Typically, the citrate-coated silver nanoparticles with an average diameter of 5 nm were prepared in a strategy as described previously.<sup>22</sup> A silver nanoparticle solution (1 mL) with the concentration of  $4 \times 10^{-8}$  M was added into 5 mL of a aminated silica sphere suspension. The solution was continuously stirred for 2 h. The suspension was removed by centrifugation, and the residue was redispersed in 10 mL of water. Then, 0.5 mL of a  $Ag(NH_3)_2^+$ solution (10 mM) and 1 mL of a glucose (20 mM) solution were added in solution subsequently. The solution was stirred at room temperature for 2 h until it became muddy brown. The silver nanoshells were recovered by centrifugation and redispersed in 10 mL of water. The treatments were repeated at least five times to control the growth of the metal nanoshell layerby-layer. To coat with the organic monolayers, the collected metal nanoshells were dispersed in a 10 mM hexa(ethyleneglycol)mono-11-(acetylthio)undecyl ether aqueous solution for 2 h.<sup>23</sup> The metal nanoshells were recovered by centrifugation and rinsed with water and ethanol for the further treatments.

**Small-Molecule Fluorophore Loading in and Release from the Metal Nanoshell.** To load the small-molecule fluorophores into the metal nanoshells, we dispersed 100 mg of metal nanoshell in 10 mL of ethanol solution containing 1 mM Rhodamine 123. The solution was continuously stirred for 72 h for the sufficient absorption of the small-molecule fluorophore in the metal nanoshells. The suspension was removed by centrifugation, and the residue was thoroughly rinsed with ethanol for the release measurements.

The release measurements were carried out in a constructed system as described in Scheme 1. Water (10 mL) was added slowly to the tube with the residual metal nanoshell sample at the bottom, and then, the sample was irradiated with a continuous laser beam with the wavelength at 420 nm and the power at 5 mW/cm<sup>2</sup>. It was observed that the loaded Rhodamine





123 was released slowly but progressively from the metal nanoshells into solution. At the interval time,  $10 \,\mu\text{L}$  of solution was take out, with slight stirring to monitor the concentration of released fluorophore in solution. The measurements were carried out on the ensemble fluorescence spectrum upon excitation at 470 nm.

**Spectral, Imaging, and TEM Measurements.** In this research, all absorbance spectra were recorded on a Hewlett-Packard 8453 spectrophotometer, and ensemble fluorescence spectra were recorded on a Cary Eclipse fluorescence spectro-photometer. Transmission electron micrographs (TEM) were taken with a side-entry Philips electron microscope at 120 keV. The samples were prepared by diluting the sample ethanol solutions to the nanomolar scale and then casting onto copper grids (200 mesh) with standard carbon-coated Formvar films (200–300 Å). The size distributions of images were analyzed with Scion Image Beta Release 2 with at least 100 spots.

The fluorescent imaging measurements were performed on a time-resolved scanning confocal microscopy (MicroTime 200, PicoQuant), which consists of an inverted confocal microscope coupled to a high-sensitivity detection setup. A single-mode pulsed laser diode (470 nm, 100 ps, 40 MHz) was used as the excitation source. An oil immersion objective (Olympus, 100×, 1.3 NA) was used to focus the laser light onto the sample and collect the emission signal. The emission passed a dichroic mirror, focused onto a 75  $\mu$ m pinhole for spatial filtering to reject out-of-focus signal, and finally recorded on a singlephoton avalanche diode (SPAD) (SPCM-AQR-14, Perkin-Elmer Inc.). Band-pass filters were used to eliminate the excitation residual and to minimize spectral crosstalk. The data collected with a TimeHarp 200 board were stored in the time-tagged timeresolved mode (TTTR) that allows every detected photon with its individual timing and detection channel information. The nanoparticles samples were diluted to the nanomolar scale in ethanol solutions and then cast on the glass coverslips for the imaging measurements.

## **Results and Discussion**

The silica spheres prepared by the Stöber method are considered to have a homogeneous size distribution.<sup>21</sup> This point was verified by the TEM image (Figure 1a), on which 90% silica spheres had an average diameter in a range of  $50 \pm 5$  nm. The surfaces of silica spheres were first aminated by 3-aminopropyltrimethoxysilane, and then the 5 nm silver nanoparticles were bound as seeds to initiate the smooth growths of metal shells.<sup>24,25</sup> The metal deposition treatments were repeated cyclically to control the growth of the metal shell layer-



Figure 1. TEM images of (a) silica spheres, (b) silver nanoshells with 10 nm thickness, and (c) silver nanoshells with 30 nm thickness.



Figure 2. Absorbance spectra of 10 and 30 nm thick silver nanoshells in aqueous solution.

by-layer. On the TEM images, the metal thickness was observed to increase with the number of treatments (Figure 1). The real metal thickness was estimated by subtracting the diameter of the silica core from the total diameter of the metal nanoshell.<sup>19,20</sup> Typically, two metal nanoshell samples with the metal thicknesses of approximately 10 and 30 nm were employed in the current research. These metal nanoshells were protected with the organic monolayers to improve the chemical stability in future treatments.

These silver nanoshells in aqueous solution exhibited an absorbance of plasmon resonance at 420 nm (Figure 2), consistent with our previous observation.<sup>18,19</sup> With the increased silver thickness, the absorbance band became more intense and broadened, but the wavelength was not altered.

We selected a type of small-molecule fluorophore that was stably absorbed in the silica gel with ethanol but eluted by water. After testing some fluorophores, Rhodamine 123 was selected in this case. To load a sufficient amount of fluorophore, the silver nanoshells were dispersed in ethanol solution with 1 mM fluorophore for 72 h. A longer time treatment was also tested, but we found that the loading number of fluorophore per metal nanoshell remained almost unchanged, indicating that the smallmolecule fluorophores were absorbed to saturation in the metal nanoshells. During storage in ethanol, no significant amount of fluorophore was released from the metal nanoshells into solution, implying that the absorption was strong. Upon excitation at 470 nm, the fluorophore-loaded metal nanoshells in ethanol exhibited a fluorescence spectrum with the maximal wavelength at 532 nm close to free fluorophore (Figure 3). However, the emission width was significantly broadened, which was due to the restrictions to the movements of loaded fluorophores in the metal nanoshells.18



**Figure 3.** An ensemble fluorescence spectrum of Rhodamine 123 free or loaded in 30 nm thick silver nanoshells in ethanol solution are shown upon excitation at 470 nm. An additional emission spectrum was measured for the silica spheres released from the 30 nm thick silver nanoshell in ethanol after the metal shells were removed by the NaCN treatment.

In the metal nanoshell particles, we questioned whether the fluorophores were bound either in the silica cores or on the metal shells. To clarify this point, we dispersed the 30 nm metal nanoshells in ethanol solution and then added several drops of 0.1 M NaCN aqueous solution to remove the metal shell.<sup>26</sup> It was observed that the color of the plasmon resonance in solution became dim progressively and disappeared completely in 5 min due to the dissolution of the metal shells. As a result, the bare silica spheres without the metal attachment were released into solution. By removing the colorless suspension by centrifugation, the collected silica spheres appeared the pink color from Rhodamine 123. By the ensemble spectral measurement, only a slight amount of Rhodamine 123 was detected in the suspension, indicting that instead of on the metal shells, most fluorophores were localized in the silica cores of metal nanoshells. This viewpoint was further supported by the observation of a strong fluorescence spectrum from the redispersed silica sphere in ethanol.

We also noticed that although the concentration of the nanoparticle in solution remained unchanged before and after the NaCN treatment, the ensemble spectral measurement showed a significant decrease of emission intensity to 2.6-fold (Figure 3). We attributed such a decrease to the loss of metal-enhanced fluorescence (MEF).<sup>27,28</sup> It is known that a near-field interaction between the fluorophore and metal can enhance the fluorescence signal from the fluorophore through the metal to the far field. The loss of the metal shell may directly lead to the loss of MEF, so that the emission intensity from solution is reduced even though the concentration of the nanoparticle in solution remains



**Figure 4.** Top panels: representative fluorescence images from the single nanoparticles recorded for both emission intensity and lifetime, (a) 10 nm thick silver nanoshell with the loaded Rhodamine 123, (b) 30 nm thick silver nanoshell with the loaded Rhodamine 123, (c) silica sphere released from the 30 nm thick silver nanoshell after the metal shell was removed by the NaCN treatment, (d) 10 nm thick silver nanoshell after the loaded Rhodamine 123 was released with the laser irradiation at 420 nm, and (e) 30 nm thick silver nanoshell after the loaded Rhodamine 123 was released with the laser irradiation at 420 nm, and (e) 30 nm thick silver nanoshell after the loaded Rhodamine 123 was released with the laser irradiation at 420 nm, and (e) 30 nm thick silver nanoshell after the loaded Rhodamine 123 was released with the laser irradiation at 420 nm, and (e) 30 nm thick silver nanoshell after the loaded Rhodamine 123 was released with the laser irradiation at 420 nm. The scales of the diagrams are  $5 \times 5 \mu$ m with 100  $\times$  100 pixels and an integration of 0.6 ms/pixel. Bottom panel: histogram of the emission intensity from (b) in the top panel, histogram of the emission intensity from (c), and histogram of the emission intensity from (e).

unchanged. The optical property changes due to the metal shells were also detected by the fluorescence imaging method. Since the concentrations of the nanoparticle in solutions were diluted to the nanomolar range prior to casting on the glass coverslips, most nanoparticles were believed to exist as individuals, and the collected fluorescent images thus contained only single nanoparticles. The representative images are presented in the top panels of Figure 4, showing that the emission brightness was reduced significantly with the dissolution of the metal shell. For each sample, we collected at least 20 emission images to analyze the data. The results are presented in the bottom panels of Figure 4, showing that the loss of the metal shell led to a 5-fold reduction of emission intensity whereas there was an increase of the lifetime from 1.5 to 5.2 ns. The decreased emission intensity was due to the loss of the metal shell, and the increased lifetime was due to an increase of the radiative rate of the fluorophore when the fluorophore-metal interaction was removed.<sup>28</sup>

In this research, the metal nanoshells with 10 and 30 nm thicknesses were selected as representative capsules to load the small-molecule fluorophores. They were respectively settled at the bottoms of tubes and immersed in 10 mL of water. The release of small molecules from the metal nanoshells was studied with irradiation by a continuous laser beam at 420 nm and 5  $mW/cm^2$ . The irradiation area was estimated to be 0.3 cm<sup>2</sup>; therefore, in 2 h of continuous irradiation, a total energy of 10 J was applied to the sample. From the color of the solution, we could observe the release of loaded fluorophores from the metal nanoshells into aqueous solution. At each time interval, an identical amount of solution was taken with light stirring, and the concentration of the released fluorophore in solution was monitored by the ensemble fluorescence spectrum. All taken solutions were detected to have identical fluorescence spectra, but the emission intensity was progressively increased (Figure 5), implying that the amount of released fluorophores into solution was increased with the irradiation time. The emission spectrum reached saturation, representing that the release reached equilibrium. On the basis of the intensity of maximal emission at 522 nm, the time profiles were created (Figure 6). The sample without light irradiation was observed in the same manner, showing a much slower release rate, indicating that the light irradiation could significantly drive the release of small molecules from the metal nanoshell capsules. The results without the light irradiation were collected as the controls (Figures 5 and 6). While taking the solution, any possible shirking or movement to the settled metal shells was strictly restricted. Thus, we believe that the achieved results in Figures 5 and 6 are reliable and comparable.

Without light irradiation, the 30 nm metal nanoshells took a longer time to reach equilibrium than the 10 nm nanoshells. It can be understood as the small molecules have to diffuse longer distances through thicker metal walls, thus taking a longer time. With light irradiation, the time to equilibrium for either sample was significantly shortened, indicating that the light irradiation accelerated the release rate. It was interesting to notice that the 30 nm metal nanoshells took only 80 min to reach equilibrium, leading to a 6-fold increase of the release rate, whereas the 10 nm nanoshells took 100 min to reach equilibrium, leading to only a three-fold increase. It means that the thicker metal nanoshells took a shorter time to reach equilibrium, reflecting that the photothermal effect by the metal nanoshell was dependent on the metal thickness. This is because the thicker nanoshells may display more intense plasmon resonances at the wavelength of laser irradiation followed by more efficient coupling with the irradiation light so that the conversion efficiency is significantly increased. This observation is consistent with the general understanding that the photothermal conversion is dependent on the absorbed energy amount and temperature increase between the laser switched-on and -off states.<sup>11,12</sup>

We also noticed that after irradiation with the laser beam, both the thicker and thinner metal nanoshells could not be repetitively used as the capsules to load the small-molecule fluorophores. Contrarily, without the light irradiation, the metal



Figure 5. Ensemble fluorescence spectra of released Rhodamine 123 from (a) 10 and (c) 30 nm thick metal nanoshells with the irradiation time under the laser irradiation at 420 nm. The spectra of controls were collected from respective (b) 10 and (d) 30 nm thick silver nanoshells without the laser irradiation.



**Figure 6.** Dependence of the emission intensity at 522 nm for released Rhodamine 123 from the 10 and 30 nm thick metal nanoshells on the irradiation time under the laser irradiation at 420 nm. The time profiles of the controls (no laser irradiation) are presented in the respective panels.

nanoshells could be repetitively used. Although the reason is uncertain, we purpose that the most probable reason is the change of tomography on the metal wall with the light irradiation. However, such a tomography change could not be observed on the TEM images. On the other hand, we know that the walls of metal nanoshells generated by the current method are assigned with the hollow pores in the nanometer sizes.<sup>29,30</sup> For the metal nanoshells used in the current research,

the pores are supposed to be relatively small, so that the metal shells can block most diffusion of small molecules. With the light irradiation, the increased local temperature in the metal nanoshells may increase the pore sizes, and consequently, the small molecules can penetrate directly through the pores on the metal walls without any block. This result indicates that as the capsules, the metal nanoshells should have the metal thick enough to make the release strongly dependent on illumination.

With light irradiation, most loaded fluorophores in the metal nanoshells appeared to be released into solution. However, we observed that there were still some left in the nanoshells without release. At the saturation state, the residual metal nanoshells were rinsed and dispersed in ethanol. The ensemble spectral measurement showed an identical fluorescence spectrum to that before the release but a reduction of emission intensity to 15% for the 10 nm metal nanoshells and 10% for the 30 nm metal nanoshells (Figure 5). The emission imaging measurements showed similar results but even weaker emission signals to 10% (bottom panel Figure 4). The results revealed that there was 10% fluorophores left in the metal nanoshells without release for the either sample, almost independent of the metal shell thickness.

As capsules for the loading and controlled-release of smallmolecule fluorophores, the metal nanoshells must have an effective payload. To study this issue, 100 mg of metal nanoshell sample was dissolved in ethanol to absorb Rhodamine 123. Because the silver shells are regarded to be continuous and dense on the silica cores, 100 mg samples were estimated to contain  $\sim 2 \times 10^{14}$  particles for the 10 nm metal shell and  $4 \times 10^{13}$ particles for the 30 nm metal shell. By the ensemble spectral measurements, the concentrations of released fluorophores in the 10 mL equilibrated solutions were estimated to be  $3.8 \times 10^{-6}$  M for the 10 nm silver shell and  $8.5 \times 10^{-7}$  M for the 30 nm silver shell. Thus, we infer that one 10 nm metal nanoshell may contain  $\sim 110$  released fluorophores. We estimated that there was 10% fluorophores left in the metal nanoshells without release. Combining the numbers of both released and unreleased, one 10 nm metal nanoshell thus contains  $\sim 120$  fluorophores and one 30 nm metal nanoshell contains  $\sim$ 130 fluorophores. Such a payload number must be regarded to be low for the capsule to load and release the smallmolecule drugs, which is due to the small sizes of the silica cores. In order to increase the payload number, we can consider increasing the core sizes to the microscale in the preparation. However, in a controlled-release to the real drugs, the capsules are expected to location-specific interact with the targets on the cells or tissues in the body. If the specially designed capsules are too large, they are expected to meet strong steric hindrances in the immuno interactions with the targets that potentially reduce the controlled release in the location-specific model. Therefore, it is crucial to optimize the sizes of metal nanoshells with high payload capability and strong location-specificity in the future.

It is known that the tissue and water have a transmission widow in the near-infrared region;<sup>31</sup> therefore, the laser beam with the near-infrared wavelength can transit the skin to come to the target sites in the body. In this research, we also irradiate the metal nanoshell samples with an alternative laser diode at 635 nm to investigate the wavelength-dependent release of the small-molecule fluorophore from the metal nanoshells. It was shown that the 30 nm metal nanoshells could initiate a significant photothermal effect, whereas the 10 nm silver nanoshells almost could not. The results at 635 nm were clearly different from those at 420 nm. The reason is that both thinner and thicker metal shells exhibit the intense plasmon resonances at 420 nm, but only the thicker metal shells display the plasmon resonances in the near-infrared region (Figure 2). This result further demonstrates that the plasmon resonance from the metal nanoparticle plays a key role in the light-driven release of small molecules from the metal nanoshell capsules.

Compared with the polymer capsules that are similar to the silica spheres used in the case, the metal shells coated on the silica cores can take on two functions, slowing down the release of captured small molecules without light irradiation and increasing the release under the irradiation. Thus, the small molecules loaded in the metal nanoshell capsules can be controlled to release with the laser beam at the specific time. As the capsules for the real release event, the nanoshells are regarded to have the release prior to reaching the tumor, but the release rates are greatly reduced. In addition, as the polymer capsules, the metal nanoshells can be functionalized by the surface reactions. Therefore, the release is localized in terms of targeting as needed.

When considering the use of metal nanoshells as potential capsules for the drug controlled release, it is important to understand the cytotoxicity of them for the risk in the applications. It is known that the silica is widely used as a food or animal feed ingredient and as a controlled delivery carrier of drugs because of its low toxicity.<sup>32,33</sup> Thus, as the core material of metal nanoshells, the silica is regarded to have a low toxicity. The cytotoxicity of the metal nanoparticle is a function of size, shape, and, most importantly, surface functionalization.<sup>34,35</sup> The silver nanoshells used in this research were protected by the thiolate organic monolayers, so that they were regarded to be chemically stable with a low toxicity. In addition, the coating layers were principally composed of PEGylation ligands that have in vitro and in vivo low cytotoxicity. Therefore, the metal nanoshells are regarded to totally have low cytotoxicity. The relative experiments will be carried out in our laboratory.

### Conclusion

We generated the metal nanoshells as the capsules to load the small-molecule fluorophores and studied the controlled release of loaded fluorophores from the metal nanoshell capsules with laser irradiation. The release rates were observed to significantly improve by the light irradiation at 420 nm, which was due to the coupling of irradiated light with the plasmon resonances from the metal nanoshells. These metal nanoshells can maximally contain the small molecules prior to interaction with the targets and release the small molecules with the laser irradiation. Therefore, the release is controlled in time. The metal nanoshells can be bound by the probes of biological interest and immuno-interacted with the targets in the body. Therefore, the release is localized as needed. In addition, the metal nanoshells have been reported to apply in thermotherapy without drugs. If these metal nanoshells are used as the capsules to load the small-molecule drugs and control the delivery of loaded drugs by light irradiation, the thermo- and chemotherapy are anticipated to take combination actions. Therefore, the therapeutic efficiency of drug treatment can be improved. We think that here is much to prove before the metal nanoshells become applicable. This work is the first step to study the controlled release of loaded small molecules from the metal nanoshells with laser irradiation.

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