Review

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Gold NanoStars: Synthesis, Modification and Application

Tianshuo Lan[1], Daxiang Cui[1,2], Tianyuan Liu[1], Xinna Yu[1], Meizhen Huang[1]

[1] School of Electronic Information and Electrical Engineering, Shanghai Jiao Tong University, Shanghai, China

[2] Institute of Nano Biomedicine and Engineering, Shanghai Engineering Research Center for Intelligent Instrument for Diagnosis and Therapy; Key Laboratory for Thin Film and Microfabrication of Ministry of Education; Department of Instrument Science and Engineering, School of Electronic Information and Electronical Engineering, Shanghai Jiao Tong University, Shanghai, China

Corresponding author. E-mail: lants762@sjtu.edu.cn; mzhuang@sjtu.edu.cn

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Abstract

Since the nanomaterial has become one of the most popular topics, gold nanomaterials have always been a research hotspot. Gold nanostars (GNSs) as one of the formations of the gold nanoparticles has stepped on the stage due to its remarkable property. By using Turkevich method, Brust method, seeded growth method and seedless-based method with proper and specific modification, GNSs could be produced for different requirements. These GNSs present various properties under a proper modification: high physical and chemical stability, high biocompatibility and the ability of modification easily. Such enormous properties and the surface plasmon resonance of GNSs could be used for various-potential applications such as surface-enhanced Raman scattering (SERS) detection, *in vivo* diseases detection and therapy, drug delivery and release and so on. All these indicate that GNS is a valuable material in biological, phenomenological and optical researches.

Keywords: gold nanostars (GNSs); modification; surface-enhanced Raman scattering (SERS); cancer treatment; targeted drug

Introduction

Since functional nano particle has become an important subject to be researched, gold nanoparticles (GNPs) always be considered as one of the highest potential materials in various areas [1–4]. By doing further researches on the property of gold, the morphology and the magnitude of the gold particles could be adjusted under different process. As shown in Fig. 1, different forms of the GNPs bring out some great differences in properties. Recently, the GNPs have been produced into the shape of sphere, cube, rod, star, flower, and so on [5–8]. All of these GNPs represent their specific properties and are used widely among most of the fields.

Among all these GNPs, gold nanostars (GNSs) had been noticed due to its special morphology. Researchers found out that all these tips formed around the GNSs could provide an enhancement for biological detection, such as surface-enhanced Raman scattering (SERS) [9–11]. All the plasmon resonance of the GNSs are concentrated on those tips, and this phenomenon would enhance the surface plasma signal which is strongly related to the surface plasmon resonance (SPR) compared to other

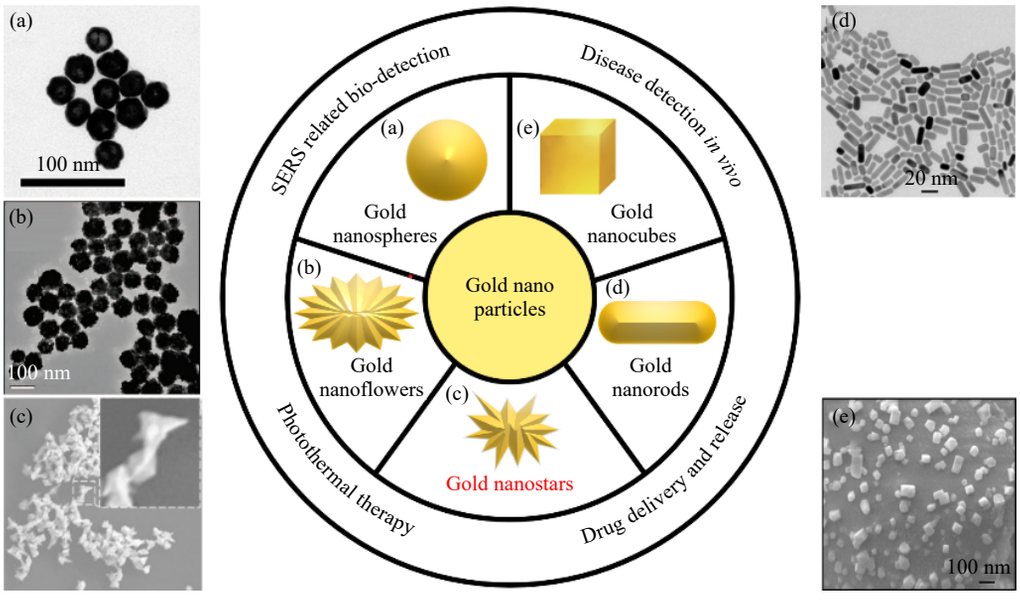

Fig. 1 Various morphologies and applications of GNPs with their SEM graphs: **(a)** gold nanospheres, **(b)** gold nanoflowers, **(c)** gold nanostars, **(d)** gold nanorods, and **(e)** gold nanocubes [5–8].

GNPs [12].

SPR as one of the most important optical phenomena of the GNSs focuses on the resonance of the metal surface. When there is a laser beam expose to the object surface, the free electrons on the surface would vibrate and affect each other [13]. Due to the property of high stability, high biocompatibility, the ability for easy functionalization and high stability, GNSs have commonly been considered as a potential material in SPR applications such as SERS based biological detection.

On the other hand, SPR effect would provide GNSs with a well photothermal property (see Fig. 2). Due to the resonance of the surface plasmon, the kinetic energy caused by the surface plasmon will transfer into the form of heat, and this phenomenon can be controlled by changing the power of the laser. By using this property to increase the temperature, GNSs could be used to deal with some medical treatments such as cancer therapy or be used for drug release [14–16].

Finally, GNSs could be easily modified. Various kinds of the functional groups are bonded to the center gold core. These functional groups provide new properties to the GNSs: increasing the biocompatibility of the GNSs, capturing the detected objects, providing more unit surface area and so on [17]. This property supports researchers to customize their own GNSs under different conditions.

Synthesis of basic GNSs

During the recent two decades, GNSs are considered as one of the most potential nano-materials no matter in medical treatment or disease detection. Therefore, the method of synthesis GNSs has been investigated for several years. Generally, Turkevich method [18] and Brust method [19] are basics technology for the synthesis of various kinds of GNPs, including GNSs. Both these two methods are based on the reduction reaction of the chloroauric acid ($HAuCl_4$). By adjusting these two methods, seeded growth method

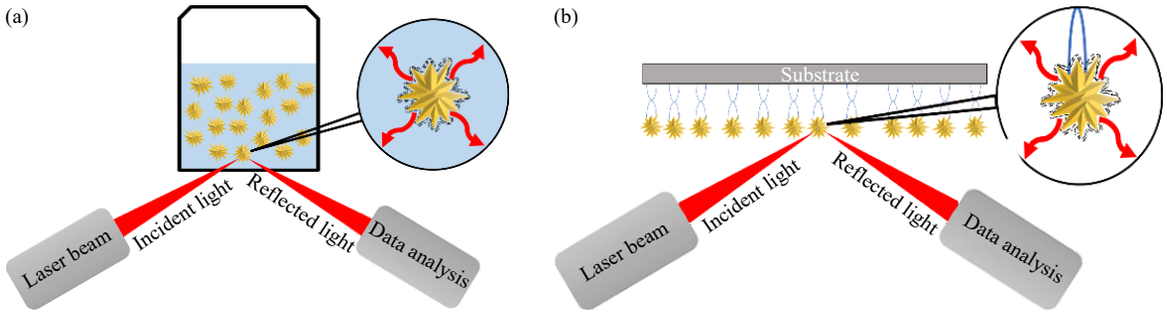

Fig. 2 The basic mechanism of the SPR effect of GNSs, **(a)** in aqueous solution, **(b)** modified on a solid substrate.

and seedless-based method were developed to produce variety nanostructures including GNSs, and these methods would provide a high quality GNS for further modification.

Turkevich method

Turkevich method was brought forward by John Turkevich in 1951 [18]. This method is one of the most commonly used methods and the beginning of the synthesis noble nanoparticles. The main step of this method is reducing the Au^{3+} into the form of Au ion. In order to prepare the gold colloidal, $HAuCl_4$ is used to be reduced and the reduction reaction leads to the nucleation of the Au ions [19]. In this reaction, the reducing agent acts an important role and there are various choices due to the demand such as sodium citrate, sodium tris-citrate, ascorbic acid (AA) and so on. Under the assistance of the reducing agent, $HAuCl_4$ can be reduced to the form of single gold atom. Most of the researchers choose to use sodium citrate as the main reducing agent because of its property for reducing the aqueous $HAuCl_4$, stabilizing the produced GNP and being a capping agent. According to this method, the final product could be a stable GNP and the magnitude of this particle is controlled under a limited range [20].

Brust method

Brust method was raised in 1994 [21]. Different from the Turkevich method, Brust method is mainly applied to produce the GNPs in the organic solution. In this method, a phase transfer agent is required to transfer the gold aqueous solution to an organic solution [22]. One of the most commonly-used phase transfer agents is tetraoctylammonium bromide (TOAB). By mixing the chloroauric acid solution with the tetraoctylammonium bromide, the aqueous gold salt can transfer to the gold ion and dissolve into the organic solution such as toluene. The next step is adding the reducing agent, sodium borohydride ($NaBH_4$), to reduce those gold ions into the single gold atom. The particle distribution and magnitude of the synthesized GNP can be customized by changing the concentration of the reducing agent and the phase transfer agents. Meanwhile, the organic solution of the synthesized environment would bring a great amount of sulfhydryl groups on the surface of the GNPs. Due to this kind of phenomenon, this kind of particles is easily to be used for further modification of specific applications.

Seeded growth method

Either Turkevich method or Brust method, the final product is regular and sphere GNPs. However, there are various kinds of nanostructures required. Thus, the seeded growth method is based on pervious methods to develop a brand-new way for producing different morphologies of the GNPs. First step of this method is same as previous two methods. By using a strong reducing agent such as $NaBH_4$, the gold salt or $HAuCl_4$ can be reduced to gold seeds. After the gold seed is produced, several components are added to the gold seeds solution under the magnetic stirring: a weaker reducing agent such as AA is added to prevent the continuous nucleation of the gold; surfactant is added to offer different growth environment for the GNPs; a structure directing agent such as silver nitrate ($AgNO_3$) is added to provide a guidance so that the branches can be grown under the required magnitude on the previous produced GNPs [23].

As shown in Fig 3, in the procedure of producing the GNSs, several components such as temperature, the amount of reducing agent, the ratio of $HAuCl_4$ and gold seed, etc. can be adjusted to change the morphology of the GNSs. Cao's work indicated that temperature, the amount of $HAuCl_4$ and the amount of reducing agent could all affect the branches of the GNSs [24]. By increasing the amounts of $HAuCl_4$, the magnitude of the center core of the prepared GNP has been macroscopically increased. Besides the magnitude, the more $HAuCl_4$ added to prepare the nanoparticle, the more branches appeared on the tip of the particles surface. Meanwhile, by adjusting the amount of the reducing agent, dopamine hydrochloride, the branches would also grow on the tip of the particles. Increasing the amount of reducing agents lead to the increasing of the particle size and the amounts of branches. Temperature is one of the most important factors to affect the growth of the GNP as well. By lifting the reaction temperature, the acceleration of the nucleation can be increased below 60℃.

In Silvia's work, the ratio between $HAuCl_4$ and gold seed is also an important part for changing the morphology of both the particle size and the length of the branches [25]. The ratio, the concentration of $HAuCl_4$ vs. the concentration of the gold seed, is defined as *R* value. Transmission electron microscope (TEM) characterization of the produced GNSs represented the phenomena: the smaller *R* value the reaction is, the smaller size of the final particle is, the

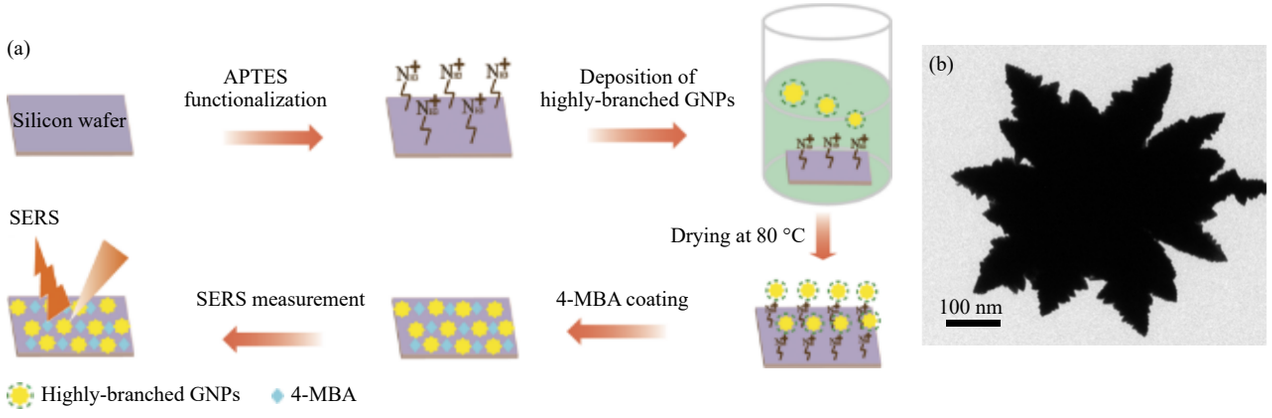

Fig. 3 GNSs produced by seeded growth method **(a)** illustration of the assembly of the GNSs substrates. **(b)** Representative TEM image of the GNSs [24].

shorter and less spikes appears on the GNSs. All these factors mentioned above could be used to customize and adjust the property of the GNSs under the required occasion.

Seedless-based method

Although the procedure of producing GNSs by the seeded growth method has been simplified compared to the Turkevich method and Brust method, there is still another method which is more convenient. This method is named as seedless-based method. Different from the seeded-growth method, the seedless-based methods only use the Au^{3+} cation from the $HAuCl_4$ solution through the whole growing reaction [26]. Both the reducing reaction and the growth of the branches of the GNSs are finished in one step, and this kind of chemical synthesis is called as one-pot synthesis [27]. All the components, such as reducing agent, growth guiding agent and capping agent attended in the reaction simultaneously in the beaker in the same step. For the seedless-based method, the reducing agent is commonly selected as the AA since it is a weak reductant. There is sufficient time for the Au^{3+} cations to contact with the AA properly in order to reach the fit morphology. By the directing of the growth guiding agent, $AgNO_3$, those branches of the GNSs could be grown under the specific requirement [28]. There are great amounts of the sections for the capping agent which used for the seedless-based method. Due to the specific requirement of the application, the choice of capping agent could be different. The selection of the capping agent provides the difference of GNSs' property, such as agglomeration or high dispersion.

In Phiri's research, the GNSs were utilized to be the substrate of the biological sensors for detecting the glucose [29]. The method to produce the basic GNSs is only related to one reduction reaction. First of all, the AA solution was added to the acidified deionized distilled H2O (ddH2O) under a magnetic stirring. After the reducing agent mixed properly in the solution, $HAuCl_4$ solution and $AgNO_3$ solution were added to the mixture solution successively. The color of the solution changed to deep blue in about 10 seconds, and this phenomenon indicated that the GNSs produced into the ideal morphology. At last, the PVP solution was added and acted as the capping agent to keep the stability of GNSs. The whole experiment would only last for few minutes. According to the comparison of the ultraviolet (UV)–visible (Vis) spectra (see Fig. 4) among different methods, seedless-based method provided the most stable result of the maximum absorption wavelength of the GNSs.

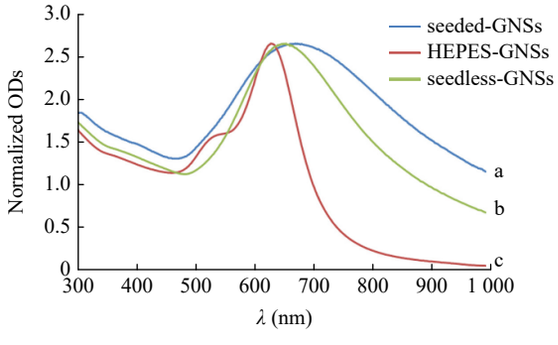

Fig. 4 Comparison of UV–Vis spectra of seeded-GNSs **(a)**, seedless-GNSs **(b)** and HEPES-GNSs **(c)** [29].

Functional Surface Modifications for GNSs

The GNSs are properly produced after the growth of the gold seed. The next step is modifying the GNSs

which is in embryo and those modifications could provide the specific property to the GNS for various applications. Sulfhydryl group, silicon coating, Polyethylene glycol (PEG) and various antibodies are the functional groups which are commonly utilized. Due to the excellent property bought by the modifications, GNSs have its potential to be used for various applications.

Sulfhydryl Group

One of the most commonly used function groups is used for building the connection between GNSs and other function groups is called sulfhydryl which is also called thiol. The basic structure of this group is R-S-H [30]. Related to the strong affinity of the sulfur with metals, sulfhydryl can be bonded of the surface of the GNSs under a covalent [31]. In Borzenkov's work, the GNSs are required to be coated with PVA films [32]. In order to reach this step, the GNSs should firstly be PEGlyation by using sulfhydryl to connect the GNSs and PEG. SH-PEG–OCH3 aqueous solution was added to the produced GNSs and the mixture was equilibrated under room temperature for 3 h [32]. This process used the sulfhydryl to modify the target functional group easily and this is only one of the great amounts of the cases. By changing functional group connected with the sulfhydryl group, the GNSs could be customized under the requirements of the application. Due to the convenience of modification and the property of connecting others, sulfhydryl group is one of the important functional groups in the modification of GNSs.

Silicon dioxide coating

Another commonly used structural-functional group is silicon dioxide (SiO_2). The SiO_2 will cover the outer layer of the GNS, and the whole nanoparticle is formed under a core-shell structure. By comparing to the PEG, SiO_2 coating could also provide a reliable modification for the GNSs. Before discussing the stability of the SiO_2 coating covered around the GNPs, Zeta potential is one of the most important parameters to determine the stability of the nanoparticle colloid. Generally speaking, if the absolute value of the Zeta potential is round or even greater than 30 mV, this colloid could be indicated as a stable colloidal suspension system [33–34]. In Straub's research, various diameters of the SiO_2@GNSs were produced to analysis the basic properties, which including the Zeta potential. The Zeta potential of the GNSs from the size of 26.1–46.4 nm was (−24.1 ± 1.7)–(−29.4 ± 0.8) mV [35]. According to these data, there is little connection between the magnitude of the GNSs and the Zeta potential. At the same time, since the absolute value of the zeta potential is close to 30 mV, this indicates that the GNSs with SiO_2 coating have a brilliant performance in stability.

Similar to the sulfhydryl, SiO_2coating could be used to build the connection between the required functional groups. Meanwhile, due to the core–shell structure, this functional group provides the GNSs with a high stability and biocompatibility [36]. One of the most commonly used methods to process the outer layer is Stöber method. Stöber method uses ethanol as the solvent to produce the small-diameter silico oxide sphere [37]. Due to the convenience in producing SiO_2, many researchers used and improved this method by producing the SiO_2 coating. In Fales's work, the prepared GNSs was resuspended into the ethanol and got ready for forming the silica coating [38]. The GNSs solution was mixed with the solution contained water and ethanol, and methylene blue (MB) and ammonium hydroxide (NH_4OH) were added to the mixture [38]. After adding addition tetraethoxysilane (TEOS) to the solution, the reaction for the silica coating proceeded. The silica cover of GNSs was produced by continuously reacting for 3 h [38]. Similar to sulfhydryl, SiO_2 coating provides a substrate for different functional groups to bond with the GNS. Meanwhile, SiO_2 coating provides a much more stable structure because of its core-shell structure. This could enormously increase the stability of the nanoparticle.

PEGlyation

PEG is a polymer which is commonly used in chemical and biological field, especially in GNPs. All these remarkable properties such as aging stability, temperature ability and bio-friendliness could be brought to the GNPs by the modification of PEG. Since there is a relationship between the value of the Zeta potential and the stability, it is necessary to detect the Zeta potential of the PEG@GNSs. In Sohrabi Kashani's research, the Zeta potential of the PEG@GNSs is (−30 ± 1) mV, and the absolute value is close to 30 mV [39]. This demonstrates the stability of the GNSs under the PEG surface modification. Meanwhile, PEGlyation could bring various

functional properties to GNSs. In Reznickova's research, it discussed the stability of the PEGylated GNPs in different directions [40]. For the aging stability, the same treatment-PEGylated GNPs were set and detected the UV absorption for a continuous 14 days. There was a red shift from 513 to 519 nm appeared for after 14 days [40]. Only a 6nm shift is acceptable for both synthesis and application of the GNPs, and this experiment result indicates the perfect aging stability of the PEGlyation brought to the GNP. On the other hand, the temperature stability of the PEGylated GNPs is an important factor in biological applications. Thus, the PEGylated GNPs was set under various temperatures including the room temperature, storage temperature and common body temperature. By comparing the UV spectra under all these different temperatures, the magnitude of the wavelength of the absorption peak barely changed [40]. This phenomenon indicated the temperature stability of the GNPs after PEGlyation. Since GNPs are required to be utilized in vivo, bio-friendliness acts as an important role for those biological applications. According to the data provided in this research, only those high concentrated (14 mg/L) PEGylated GNPs could not reach the 100% metabolic activity for those cytotoxic substances. For the 1 and 7 mg/L PEGylated GNPs, all those poisonous substances could reach a full metabolism [40]. Due to all these properties related to the biocompatibility, PEGlyation is strongly bonded with GNPs including GNSs, and more and more application used PEGlyation as a capping agent. As one of the members of the GNPs, GNSs also carry those excellent properties caused by the PEGlyation. In Shiraishi's work, the toxicity of the PEG had been indicated as harmless *in vivo* since there is no pathological abnormality of the examination of organs and tissues under the PEG environment [41]. At the same time, the immunogenicity of the PEG could be excellent enough for drug delivery and bioconjugation [42]. Due to the property of low toxicity, outstanding immunogenicity and even hydrophily, PEGlyation is getting more and more popular in the modification and this technology is used to modify the GNSs. In Navarro's work, the GNSs were required to be utilized for intracellular uptake [19]. In order to fit this requirement, PEGlyation of the GNSs was important for this application. By adding the $PEG_{2000}-SH$ the solution to the GNSs under the ratio of 1:9 and continuously heating to 70 for 48 h, the nanostars were properly modified. This method used the sulfhydryl as the connection between PEG and GNSs, and the PEG group would provide a biocompatible polymer layer for further application [43]. Combining the property of GNS and the property of the function group—PEG, this nanoparticle is capable to be used in the application of drug delivery, antibody detection and nucleic acid etc.

Antibody functionalization

In medical treatment and detection, the modification of the antibody is getting more and more acknowledged. Due to the specific property of the GNSs, researchers study the combination between the modification of antibody with GNSs. By using this kind of GNSs, the targets could be easily detected and located in a simple way which means a lot in medical detection and therapy. In Kafshgari's work, the modified antibody of the GNSs were used for targeted delivery of RNA therapeutics [44]. Before the medication, the GNSs were prepared under PEGylation and added into the Thiol-PEG5kDa-acid (SH-PEG5kDa-COOH) which provides both PEG and sulfhydryl bond. This PEGylated GNSs would be conjugated with the employ epithelial cell adhesion molecule (EpCAM) antibodies. Liang's work is about the application of the GNSs modified with CD44v6 monoclonal antibody [14]. Similar to the work of Kafshgari's, the pretreatment of the GNSs was the PEGlyation and thiol had been already modified on the surface of this nanoparticles during the producing process of GSNs. 3-(3-dimethylaminopropyl)-carbodiimide (EDC) and N-hydroxysulfosuccinimide (Sulfo-NHS) were added to the previous GNS solution, and the pH of the whole solution was adjusted to 7.0 [14]. Finally, the mouse anti-human CD44/CD44v6 antibodies were added under the room temperature for 2 h with stirring [14]. According to the cases represented above, more and more various kinds of the antibodies were figured out which could be modified on the GNSs. According to the excellent photothermal and biocompatibility of substrate, these modified GNSs are widely used in cancer therapy and disease detection.

Application of GNSs

GNSs are widely used in different applications due to the highlight properties of easy modification for

different targets. Under these modifications, GNSs could achieve various biological and optical properties for further using.

SERS related bio-detection

Surface-enhanced Raman spectroscopy (SERS) had been discovered by Fleischmann in 1974, and in Fleischmann's work, the rough surface of the silver enhanced the Raman signal of the pyridine [45]. This research turned on the gate which is using the rough noble metal's surface or the nanoparticles of noble metal to enhance the Raman signal of the measured objects. As one of the possible materials in SERS, GNSs had been researched for recent several years and turn to be a hot spot in medical detection. In Hameed's work, the well-prepared GNSs were used to detected the breast cancer cells [46]. By controlling the concentration of the silver nitrate used in producing the GSNs, the monography of the spikes could be adjusted. By relating to the property of the GNSs, the longer spikes of the GNSs are, the more efficient the signal could be detected, and the Raman signal of the detected targets could be enhanced [28]. Under this phenomenon, the intensity of the specific Raman spectra changed with the changing of the concentration of the human MDA-MB-231 cancer cell [46]. Meanwhile, the biocompatibility and the cytotoxicity had been indicated as harmless to biological environment. A proper concentration of the silver nitrate could control the cytotoxicity to the MDA-MB-231. This is just one of the cases which used SERS to detect the disease, and there is a great possibility to detect more kinds of diseases by adjusting the modification of the surface GNSs.

Disease detection *in vivo*

Since the PEG modification provides a great biocompatibility to the GNSs, the toxicity caused by the gold could be controlled under a safety level for biomedical. Due to this reason, it is possible to use GNSs in vivo detection or therapies. Among all the diseases detection, cancer always attract people's attention. As one of the diseases has the highest fatality rate among the whole world, researchers still find the way to detect the cancer tissue in order to provide proper treatment at an early stage. GNSs act as a tool to detect the cancer tissue due to its property of sensitivity and specificity. In Liang's research, the modified GNSs were used to locate by a highly efficient accumulation of the GNSs around the breast cancer tissue (see Fig. 5) [47]. Due to the customization of the GNSs, GNS@ICG-Ab was produced to catch those tumor cells and all these tumor-GNS groups would combine together for

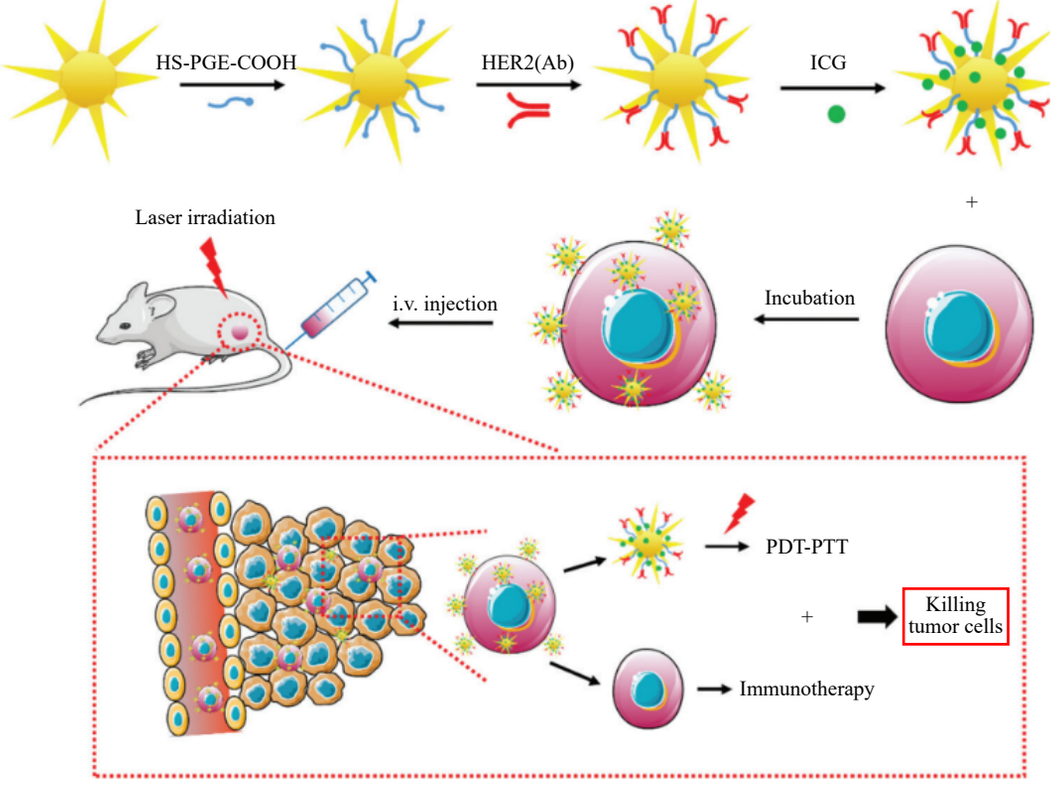

Fig. 5 Schematic illustration of nanoplatform construction and combination therapy for tumor [47].

further detection.

At this moment, those groups could be detected through fluorescence, photoacoustic (PA), and computed tomography (CT) imaging observations. In Zhang's research, as shown in Fig. 6, the modified GNSs were utilized as a CT contrast agent for CT imaging of the tumor [48]. Similar to the common process to locate the tumor tissue, the ASCE-R probe modified on the GNSs was internalized the tumor cell by the recognition receptor. 72 hours after injecting the GNSs to the tumor mouse, the 808 nm laser was utilized to excite the GNSs. Due to great photothermal property of the GNSs, the CT signal of the tumor inside the mouse was apparent enough to indicate the diseased region [48]. Moreover, by combining the GNSs to the specific antibody of the detected diseases with those bio-friendly modifications, this kind of particles easily catch the target objects. Meanwhile, the GNSs have the special morphology, star shape, these sharpy tips provide more signal compared to other gold nano materials, and this property greatly increase the accuracy and sensitivity during detection. Since GNSs has the effect of SPR, GNSs could be excited by the near-infrared laser, this provides a way to locate those GNSs through human's skin.

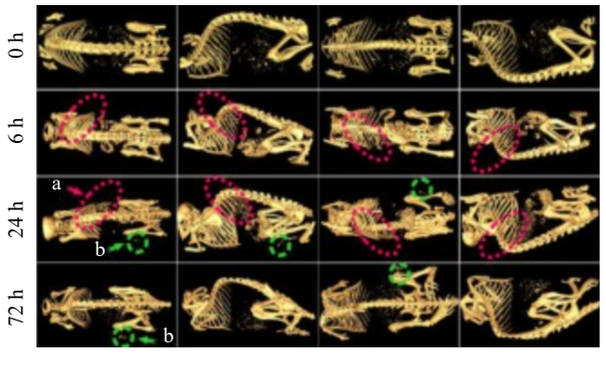

Fig. 6 CT imaging at different times of nude mice after injection of the ASCE-R positive probe, a: spleen (marked in red), b: tumor (marked in green) [48].

Photothermal therapy

Actually, the detection of diseases is not the end of the whole process. GNSs would keep staying around the tumor and act as another role to eliminate those pathological tissue. After exciting by the near-infrared laser, the heat caused by the resonance of GNSs is used to kill the tumor tissue. By changing the power of the output laser, patients would have a safe treatment. In Pan's research, as shown in Fig. 7, the GNSs were modified to fit the *in vivo* environment and connect directly to the breast cancer tumor. The particles which modified as GNSs-dPG(RA)-HA would cover around the tumor tissue and be excited under a near infrared laser [49].

In order to figure out the perfect wavelength of the laser generator, the maximum absorption peak of GNSs needed to be found out, and it was nearly at the wavelength of 800 nm [50]. The closer wavelength between the actual excited laser and the absorption peak of the GNSs, the higher utilization efficiency of the laser could be. According to this reason, an 808-nm laser generator at 1.0 W/cm^2 was used to expose those prepared GNSs to gain the heat for increasing the temperature. Under this effect caused by the laser, those tumor tissues had been killed under a controlled temperature and the tumor volume of the test specimen had been decreased compared to the control sample group. The tumor volume normally could be controlled under 100 mm^3 for 14 days, and this result indicated the success of using the modified GNSs for breast cancer since the control sample's tumor volume reached to round 500 mm^3 for 14 days [49]. This research was just one of the papers using GNSs for medical treatment and proved GNSs' ability to provide a safe condition for eliminating the tumor tissues *in vivo*. Meanwhile, by combining another application, biological detection, it could be more precise and accurate to design the therapeutic regimen of the patient.

Drug delivery and release

Beside the photothermal therapy, the other way to use GNSs in medical therapy is targeted drug. Both these two methods are strongly related to the SPR effect. By providing a near-infrared laser which has the wavelength fit the highest peak of GNSs, the GNSs would produce a controllable heat. What's different for the targeted drug is usage of this heat. In the application of targeted drug, the heat is one of the factors which would be used to change the tumor microenvironment so that the transportation and release of the drug could be controlled.

Commonly, there are two methods for carrying the drug by GNSs. One of the methods is directly modified the specific drug on the surface of the GNSs, and the other one is using a carrier to assist the drug transfer and releasement. In Tian's research, the mitoxantrone (MTX) was the drug requireed to be carried to the tumor cells, and MTX was modified on

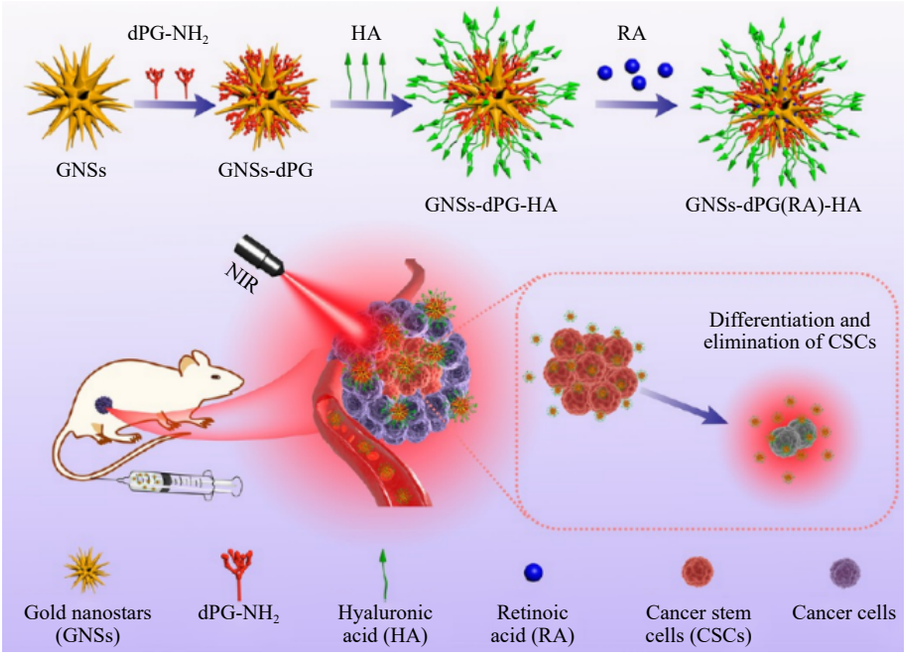

Fig. 7 Synthetic scheme of RA-loaded GNSs-dPG for targeted photothermal therapy in breast cancer stem cells [49].

the surface of the GNSs. After the PEGlyation of the GNSs was produced, MTX would be modified with the carbodiimide chemistry assisted by N-hydroxisuccinimide (EDC/NHS coupling reaction) between the carboxylated PEG terminal [9]. By using a 785-nm laser, the GNSs would be excited and released the anticancer drug around the pathological tissue. Meanwhile, the laser could cause the SPR effect of the GNSs which provide the Raman signal of the MTX@GNSs [9]. By utilizing of the Raman signal for the imaging spectroscopy, the level of the drug releasement could be monitored to reach the goal as drug sustained release (see Fig. 8).

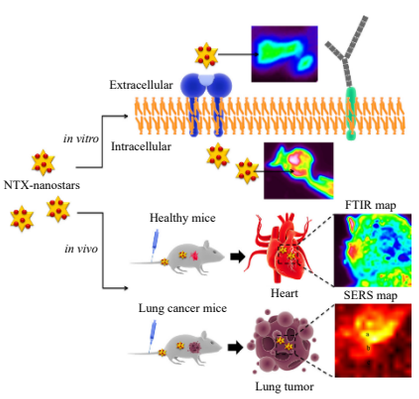

Fig. 8 Gold Nanostars for theranostics: intracellular and *in vivo* SERS detection combined with real-time drug delivery using plasmonic-tunable Raman/FTIR imaging [9].

On the other hand, there are other modification methods which could also be utilized for drug delivery and release. In Miao's research, the GNSs are modified to be used for a treatment dealing with the combined cancer [51]. All the preparations are similar to the photothermal therapy such as GNSs modification, combination with tumor and near-infrared excited. As shown in Fig. 9, after the A-GNS/DNA/DOXs combining with the tumor cells and being exposed under near-infrared laser, the combined i-motif DNA which is modified on the GNSs and formed by i-motif strands S1 and S2 would be broken into single S1 and S2 strands [51]. This would cause the pH of the environment changed to be more acidic, and the DOX modified on the GNSs would release to the tumor cells. As an anticancer drug, the released DOX could easily break the DNA chains of the cancer tumor and those tumors would lose the function of lethality to the host.

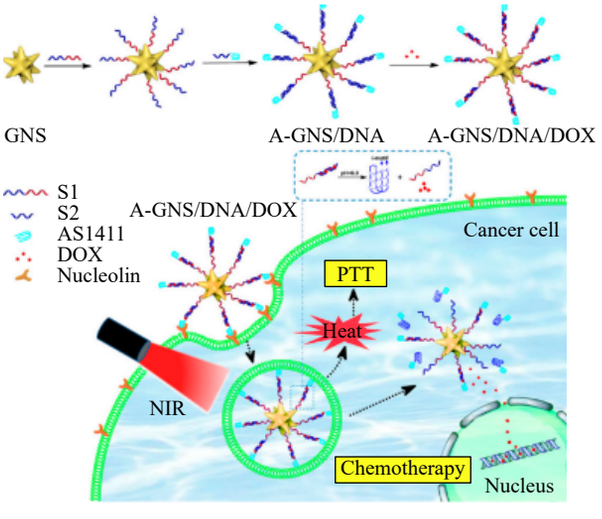

Fig. 9 Facile preparation of the near-infrared and pH dual-responsive nanocarriers, A-GNS/DNA/DOX, and the applications in combined chemo-photothermal cancer therapy [51].

Therefore, the modified GNS is a powerful tool for no matter drug delivery or drug release. By combing with previous applications, GNSs could provide an integrated diagnosis and treatment scheme for patient to overcome the cancer.

Conclusion

As a high potential nano material, GNSs have a great amounts of flash points. By using the improved seeded growth method, GNSs could be properly produced under few steps as the preparation for further modification. Various kinds of functional groups could be modified on GNSs' surface in order to reach different properties and demands. The produced GNSs are commonly used in SERS detection, disease detection, photothermal therapy and targeted drugs. All these applications certify the value of GNSs in optics and biology applications.

Although GNSs performed perfectly, but there are still many challenges which are needed to be improved: the SERS signal of diseases detection should be more precious and the noise signal needs to be lower; the method to control the movements of GNSs in vivo to directly reach the targeted area of tumor tissue; GNSs adjusted to a highly efficient probe for carrying multi-targeted drugs per time. By designing different structure and modification of GNSs, there should be a way to overcome all challenges and GNSs could be used for more conditions.

CRediT Author Statement

Tianshuo Lan: data curation, investigation, methodology, visualization, writing original draft, writing–review, and editing. **Daxiang Cui:** conceptualization and supervision. **Tianyuan Liu:** formal analysis, investigation, project administration, and supervision. **Xinna Yu:** formal analysis and investigation. **Meizhen Huang:** conceptualization, project administration, and supervision.

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Conflict of Interest

The authors declare that no competing interest exists.

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