



Synthesis, optical properties and phototherapy applications of gold nanostars

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Abstract

Phototherapy is a type of medical treatment that involves exposure to ultraviolet-visible (UV–Vis) region or near-infrared (NIR) region light to treat certain medical conditions. Compared to other treatment methods such as chemotherapy and radiotherapy, it attracts a lot of attention today due to its lower cost, more effect on the tumor cell, and less side effects. Today's clinical therapy research shows that combining chemotherapeutic methods and phototherapeutic methods on a single nanostructure increases the therapeutic effect that each method alone has, and this is even more effective in destroying cancer cells. The emergence of nanomaterials recently opens up new opportunities to increase therapeutic efficacy and overcome limitations in current phototherapy techniques. Gold nanostars (GNSs) are a kind of promising photothermal agent recently in the biomedical field with its strong absorption in the NIR field, high photothermal conversion efficiency, excellent photothermal stability, and biocompatibility. In this study, the synthesis methods, optical properties of GNSs, and their current studies on cancer diagnosis and treatments are summarized.

Keywords Gold nanoparticle · Gold nanostar · Photothermal therapy · Photodynamic therapy · Cancer

Abbreviations

CS	Chitosan	PAI	Photoacoustic imaging
CT	X-ray computed tomography	PDT	Photodynamic therapy
FDA	Food and Drug Administration	PEG	Polyethylene glycol
GNCs	Gold nanocages	PET	Positron emission tomography
GNP	Gold nanoparticle	PS	Photosensitizer
GNPs	Gold nanoparticles	PTT	Photothermal therapy
GNRs	Gold nanorods	SERS	Surface-enhanced Raman spectroscopy
GNS	Gold nanostar	SPR	Surface plasmon resonance
GNSs	Gold nanostars	TEM	Transmission electron microscopy
GSH	Glutathione	UV–Vis	Ultraviolet-visible
LSB	Lauryl sulfobetaine		
LSPR	Localized surface plasmon resonance		
MB	Methylene blue		
MPS	Mononuclear phagocytic system		
MRI	Magnetic resonance imaging		
NIR	Near-infrared		
NPs	Nanoparticles		
PA	N- (3-aminopropyl) methacrylamide hydrochloride		

Highlights

- Phototherapy is a type of medical treatment that involves exposure to ultraviolet-visible region or near-infrared region light to treat certain medical conditions
- Gold nanostars are a kind of promising photothermal agent recently in the biomedical field
- The emergence of nanomaterials recently opens up new opportunities to increase therapeutic efficacy and overcome restrictions in current photothermal therapy and photodynamic therapy applications

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Introduction

Cancer occurs as a result of excessive and uncontrolled proliferation of any group of cells in the body. While the World Health Organization data showed about 18.1 million new cancer cases in the world last year, 9.6 million people died from cancer [1]. Cancer is also a personal disease, although there are more than 100 known types of cancer and standard approaches have been developed for certain types of cancers. The early diagnosis of cancer is very important in the success of cancer treatment [2, 3]. Today, some imaging techniques such as X-ray computed tomography (CT) [4], magnetic resonance imaging (MRI) [5], positron emission tomography (PET) [6], near-infrared (NIR) fluorescence imaging [7] and photoacoustic imaging (PAI) [8, 9] are used to diagnose cancer.

NIR region light has unique advantages like high sensitivity and negligible irradiation risk compared to visible region light [10, 11]. For this reason, NIR fluorescence imaging is highly used in cancer detection [12]. Unfortunately, NIR fluorescence imaging has disadvantages such as limited spatial resolution and limited depth of tissue penetration [13]. As a new imaging method, PAI is a biomedical imaging method based on photoacoustic effect [9, 14]. Overcoming penetration limitations and high spatial resolution have some advantages over NIR fluorescence imaging, while the sensitivity needs to be further improved [15, 16] NIR fluorescence imaging and PAI methods are used together to provide sufficient information in cancer diagnosis [17, 18].

The primary purpose of cancer treatment is to select and destroy diseased tissues without causing any damage

to normal tissues. Modern cancer treatment methods commonly used today are chemotherapy, radiotherapy and surgical methods [19]. These methods have many disadvantages such as weakness, nausea and vomiting, skin and nail problems, intestinal problems, infection, blood and clotting problems, limited range of effects, and causing drug resistance [20, 21].

Phototherapy is a method in which UV–Vis or NIR region light is used for therapeutic purposes. Compared to other cancer treatment methods such as, chemotherapy, and radiotherapy, it attracts a lot of attention today because of its lower cost, more effect on the tumor cell and fewer side effects [22–24]. Phototherapy can be examined under two main titles as photothermal therapy (PTT) and photodynamic therapy (PDT). Photothermal therapy (PTT) is a therapeutic method whereby cancers are ablated by the heat generated from absorbed NIR light energy (Fig. 1) [25–27]. The substance used in PTT is an optical absorbing agent that can absorb strongly in the NIR region and can destroy the cancerous cells by effectively converting the photo energy within it to NIR irradiation [28].

PDT, is based on the principle of exposing the photosensitizer (PS) selectively accumulated in the target tissue to visible light of suitable

wavelength. In the presence of molecular oxygen, free radicals formed as a result of light activation of PS and singlet oxygen destroy cells in the targeted region by interacting with many biological molecules such as oxygen, lipid, protein, and nucleic acids (Fig. 2) [29, 30].

Today, clinical therapy researches show that combining chemotherapeutic methods and phototherapeutic methods on a single nanostructure increases the therapeutic effect that each method alone has, and this is even more effective

Fig. 1 Schematic illustration of the photothermal imaging system set up by Zhou and coworkers [25]

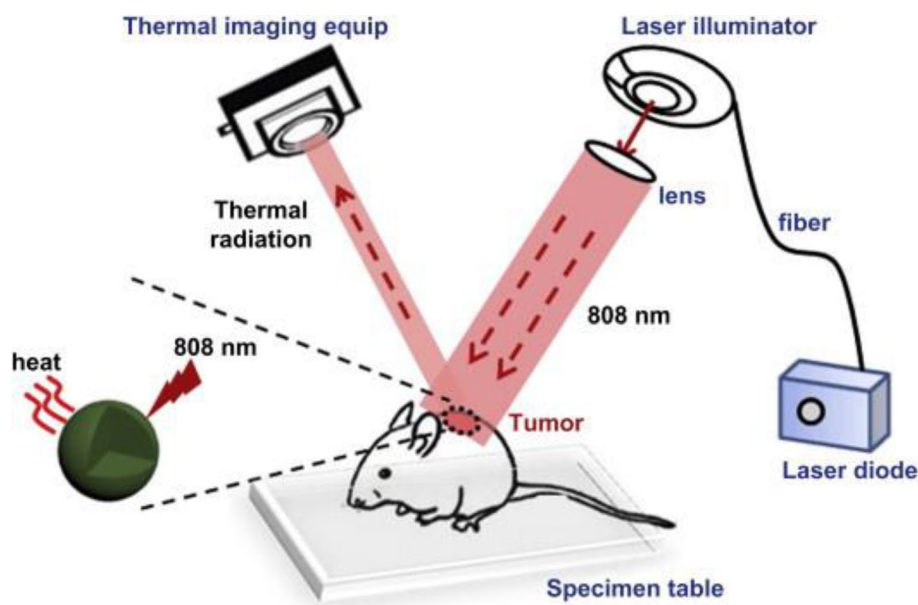
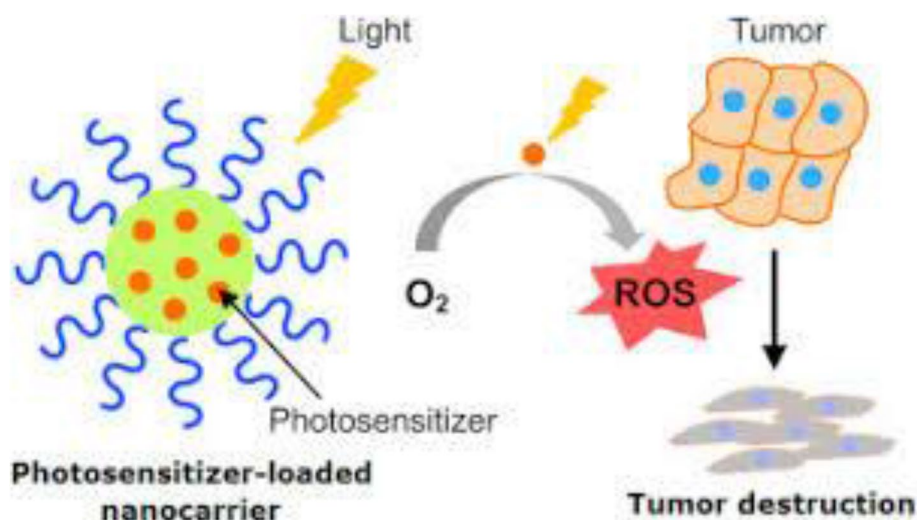


Fig. 2 Schematic illustration of the photodynamic therapy [30]

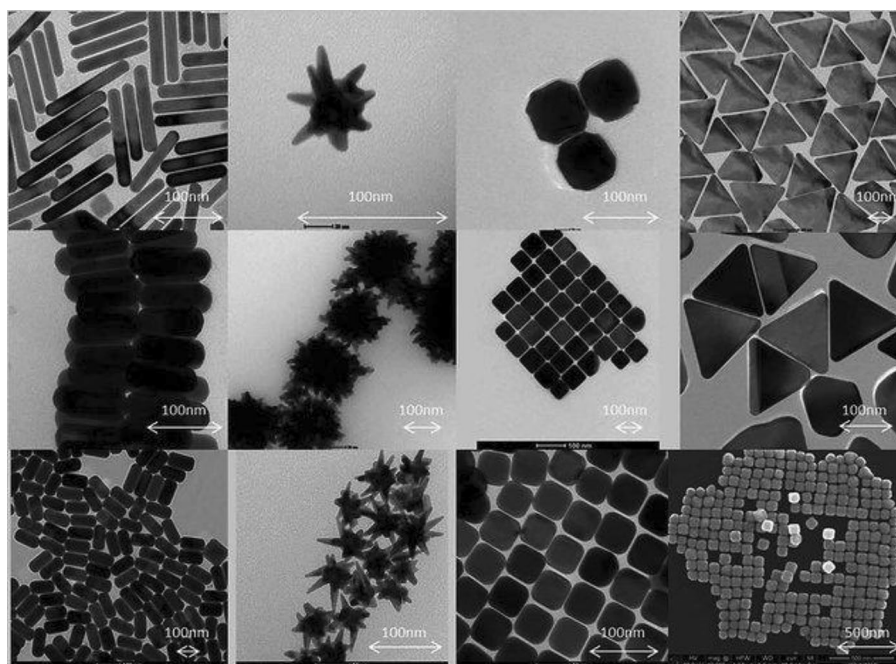


in the destruction of cancer cells [31, 32]. Because, the increase in temperature in tumor microenvironment causes drug release into the tumor cells and increases the toxic effect of the drugs [33]. The emergence of nanomaterials recently opens up new opportunities to increase therapeutic efficacy and overcome restrictions in current PTT and PDT applications [34, 35]. Nanomaterials designed for cancer treatment are very important in terms of their good water solubility, biocompatibility, high therapeutic efficacy, low toxicity, and selective collection in cancerous cells, less harm to other healthy cells [36]. The use of NIR region in these nanomaterials in the wavelength range of 700–1100 nm is preferred in terms of high tissue permeability and no harm to healthy cells [37, 38]. For

this reason, studies on functional NPs that can effectively load drug molecules and emit with NIR light activation are increasing.

Gold nanoparticles (GNPs) are a promising photothermal agent recently in the biomedical field with their strong absorption in the NIR field, high photothermal conversion efficiency, excellent photothermal stability, and biocompatibility [39, 40]. GNPs can be obtained in shapes (Fig. 3) such as spheres [41], rods [42], stars [43], and have found many application areas in biomedical systems. Gold nanostars (GNSs) are highly effective in converting light into heat, with multiple sharp ends, among anisotropic GNPs [44]. These features have been confirmed experimentally and theoretically in many studies [45] (Fig. 4).

Fig. 3 Library of nanoparticle shapes: TEM and SEM micrographs of gold nanoparticles by Dr Željka Krpetić (CBNI, UCD) [41]



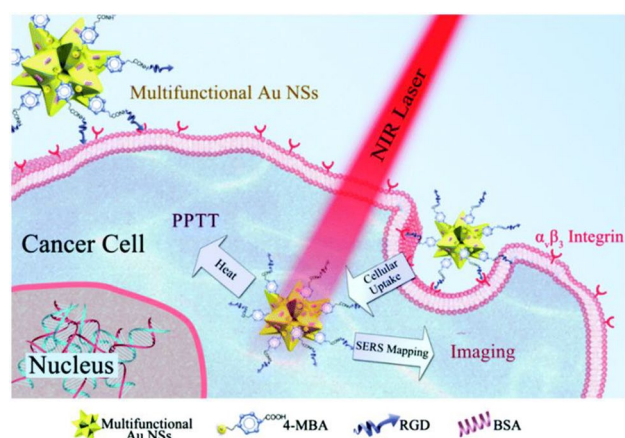


Fig. 4 Schematic illustration of the structure and application of multifunctional GNSs synthesized by Song and co workers for cancer cell-targeted NIR SERS-imaging and PTT [58]

Gold nanoparticles (GNPs)

Over the centuries, the fascinating natural luster of gold has attracted much attention. Gold has an intense yellow color because it absorbs light in the blue range of the electromagnetic spectrum. However, by changing the size and shape of gold particles in nanoscale, it turns pink, violet, and blue [46]. The interesting optical properties of GNPs are caused by the vibration of free electrons in the structure of these NPs when exposed to electromagnetic radiation. When the vibration frequency of the incoming light is compatible with the oscillation frequency of the free electrons, the light absorbs the maximum, which is called surface plasmon resonance [47]. GNPs are widely applied in colorimetric experiments because of their strong localized surface plasmon resonance (LSPR) and outstanding damping coefficient with a wide range of regions from visible to infrared [48]. It can be synthesized in various forms such as gold nanorods (GNRs), gold nanostars (GNSs), and gold nanocages (GNCs) [49].

Gold nanostars

Nanostars are pointed nano-objects that come out of a spherical core [50]. Recently, as a kind of new material, GNS has gained much more attention due to its circular structure with sharp protruding branches. Sharp-tip anisotropic NPs can provide significantly larger near field enhancements, called "hot spot" regions at the sharp ends [51, 52]. The light intensity can be increased up to 10^6 times in hot spot areas [53]. The importance of hot spots for the production of hot carriers has been confirmed by various experimental and theoretical studies [54]. Recently, it has been proven that hot spots can have a significant photothermal effect by loosening hot electrons [55]. Therefore, photothermal production as well

as more efficient hot carriers can be expected through LSPR stimulation in anisotropic GNS. GNSs with very sharp branches showed stronger SERS increase with the "lightning rod" effect compared to spheres, cubes and bars GNPs [56, 57]. The applications of bare GNSs are very limited due to its low solubility in water and its aggregation easily. To increase the stability, monodispersity, and water solubility of naked GNS, the GNS surface can be modified through molecules such as PEG, and BSA, [58, 59] through the Au-S bond. Also, GNSs have great applications in photonic catalysis, sensing, plasmonics, and building blocks, PTT, PDT, and biomedical engineering.

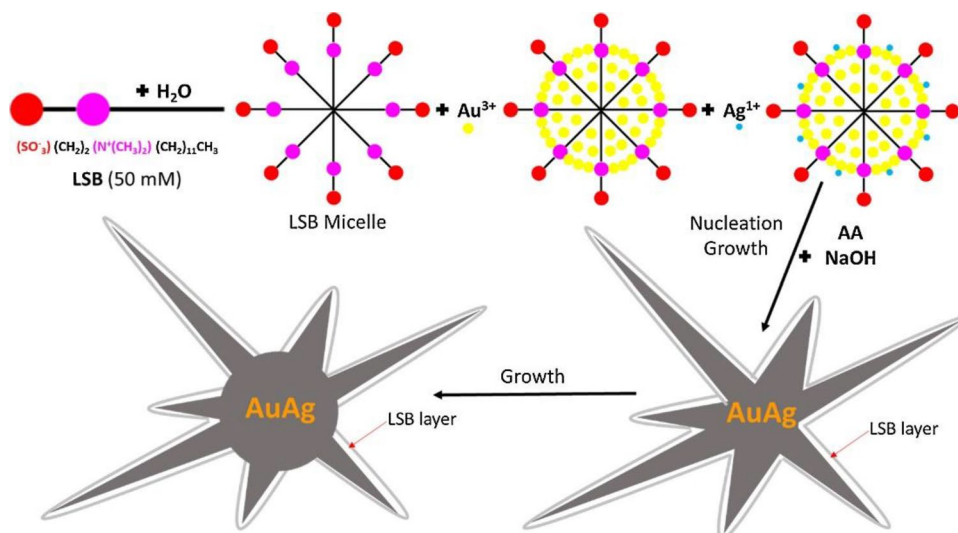
Synthesis methods of GNSs

The seeded growth method, and seedless homogeneous nucleation methods have been developed for the synthesis of GNSs. The seeded growth method usually includes seeds (small spherical NPs), silver ions (Ag^+), shape-guiding agents, and additional gold ions [50, 60]. The resulting nanostar size and the sharpness, multiplicity, and size of the ends are highly dependent on the number of seeds, reducers, and Ag concentrations. The presence of silver in the growth solution is also very important for the formation of nanostars; NPs do not form when there is no silver [61]. Reduction in seedless growth, which is a simple and fast synthesis method, is performed in a single step in which both nucleation and growth occur together. This method is being explored as a way to overcome complications in two-stage seeding growth [62–64].

Josep and co-workers [50] have developed a single-step seedless green method for the synthesis of gold-silver (AuAg) spiny branched nanostars where the main ingredient is 90% gold (Fig. 5) In this method, zwitterionic surfactant lauryl sulfobetaine (LSB) was used in the synthesis of bimetallic nanostars. It has been noted that the LSB concentration plays an important role in determining the shape and size of nano objects and a minimum concentration of 50 mM LSB is required for the formation of pointed branched nanostars. This method is a seedless approach that does not need a surfactant. It not only reduces the synthesis time but also removes the step of eliminating the surfactant.

Phan et al. have also developed a new method for preparing GNS using environmentally friendly materials [65]. In this one-step method, chitosan (CS) was used as a stabilizer, vitamin C as a reducing agent and water as a solvent. In the study, it was stated that in the synthesis of GNS, the particle size can be controlled by CS. Vitamin C is a good antioxidant derived from citrus and other vegetables, it can reduce the Au (III) ion to the Au (0) atom [66]. CS can be used to increase the stability of unstable NPs because it has properties such as multiple reactive functional groups, high positive charge, biodegradability, biocompatibility,

Fig. 5 Schematic representation of the proposed micelle formation process using 50 mM LSB and the nanostars that are expected to grow over the micelles by Joseph and coworkers [50]



nontoxicity, and low cost [67]. CS is a linear polymer that consists of glucosamine and acetylglucosamine units that act as a polyelectrolyte with a high positive charge density in low pH solutions. Therefore, changing pH levels can affect the behavior and properties of CS. Low environmental pH increases the positive charge in CS [68]. In this study, to evaluate the effect of pH on GNS formation, three experimental conditions with constant CS concentration (0.05 %) and pH = 1, 3, and 5 were determined. It was determined that gold structures with indeterminate ends were formed in pH = 5 and pH = 3 solutions, and the absorption of gold solutions was not in the NIR region but at 570 nm and 605 nm, respectively. However, in experiments carried out at pH 1, it was stated that the star structure is seen and it has a strong absorption at 750 nm. The study also examined the effect of CS concentration on the gold nanostar structure. TEM images of NPs obtained by increasing CS concentration from 0.05 to 0.9% were taken. When the CS concentration is 0.05% the nanoparticle size obtained is 225.9 ± 52.9 nm, while the CS ratio is 0.9%, it is 111.3 ± 56.2 nm, and as the CS concentration increases, the ends are not shorter and sharper and the NIR region. They stated that the absorption was weakened.

Gold nanostars in cancer diagnosis and therapy

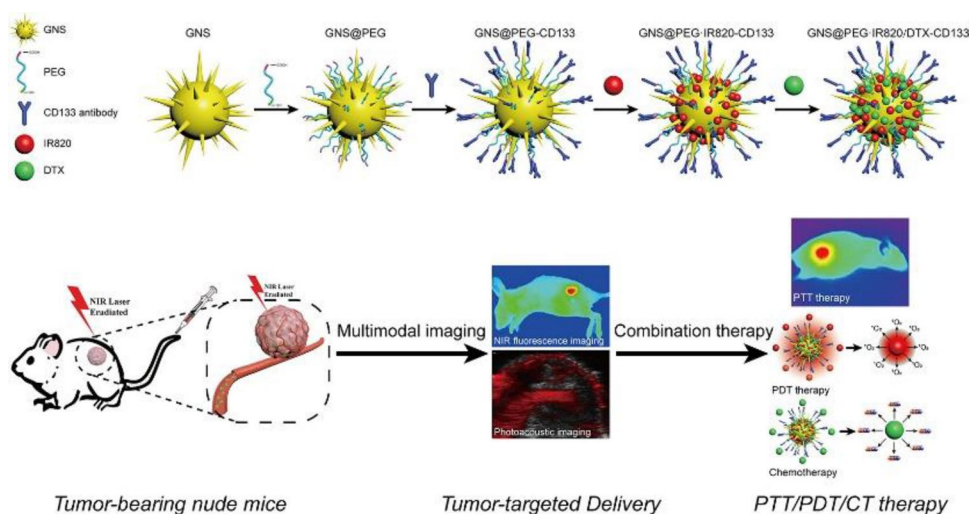
GNSs can produce singlet oxygen [69] through various mechanisms such as various photochemical pathways [70] and hot electron emissions [71]. Wang et.al [72] demonstrated that, GNSs under NIR light irradiation can exert not only cancer photothermal therapy via heat production but also photodynamic therapy via generation of reactive oxygen species. As a result of this study, GNSs were able to enter the

cytoplasm as well as nuclei of human breast michigan cancer foundation-7 (MCF-7) cells, and under NIR light irradiation, GNSs caused more severe DNA damage, arrest the cell cycle in G0/G1 phase, and reduce more cellular glutathione level, causing more severe apoptosis and cell death in vitro. Two different sizes of GNSs were synthesized by Duong et al. [73] and their surfaces were coated with N-(3-aminopropyl) methacrylamide hydrochloride (PA) to examine the ability to produce singlet oxygen. In the study, it was found that the production of singlet oxygen is more than multi-tailed and large size GNS, that methylene blue (MB) functionalized GNSs produce more singlet oxygen than MB, also only PA coated GNSs are used for the production of singlet oxygen. Fales and coworkers developed a theranostic system combining Raman imaging and the photodynamic therapy (PDT) effect. The theranostic nanoplatform was created by loading the photosensitizer, protoporphyrin IX, onto a Raman-labeled gold nanostar [74]. In their study, Tan et al [75] loaded the IR820 and DTX by functionalizing the gold nanostar with CD133 antibody via PEG. (GNS @ IR820/DTX-CD133). It is stated that the synthesized nanoparticle is approximately 120 nm in size and the surface plasmon peak is at 810 nm (Fig. 6).

In vitro and in vivo experiments were performed on human castration resistant prostate cancer PC3 cell line. The in vitro therapeutic potential of the GNS @ IR820/DTX-CD133 nanoparticle was determined by evaluating the photo-thermal effect, singlet oxygen production, cellular uptake capability, biocompatibility, and killing of cancer cells. The results showed that the GNS @ IR820/DTX-CD133 NPs were also stable in water, and also had excellent targeting-tumor capability and exceptional tumor affinity after NIR laser-mediated treatment.

Nanoprobes used in PAI are becoming increasingly important in the diagnosis and treatment of various

Fig. 6 Schematic illustrations of the synthetic route of GNS@IR820/DTX-CD133 as the synergistic PTT/PDT/CT nanoplatform for CRPC under the monitoring of multimodal imaging by Tan et.al. [75]



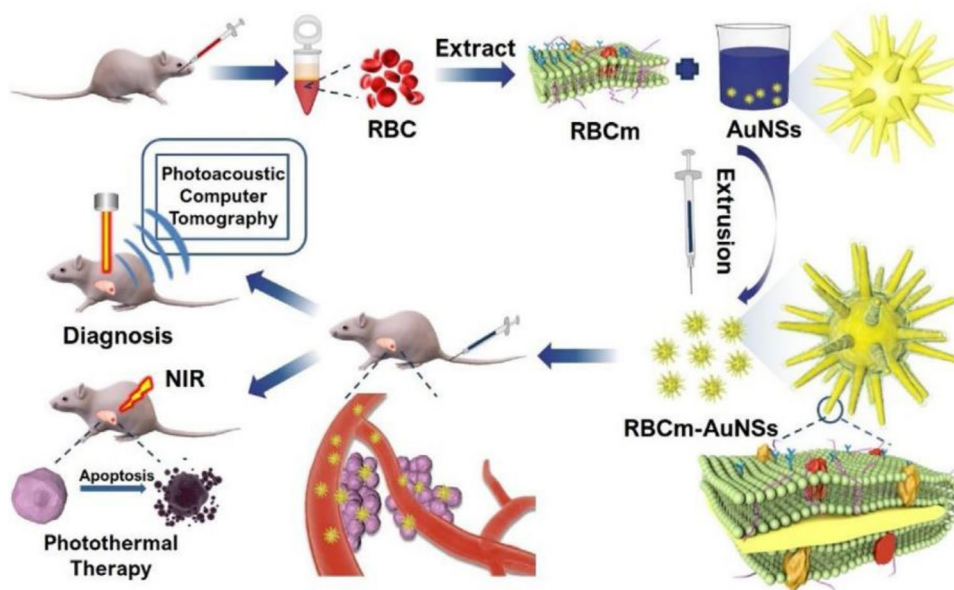
diseases, especially liver cancer [76]. However, the mononuclear phagocytic system (MPS) exhibits a significant barrier to probe use by preventing probe buildup in the liver. To overcome the MPS clearance, Huang et al. [76] synthesized a biomimetic probe composed of golden nanostars camouflaged with an erythrocyte membrane (Fig. 7). The experimental results have shown that the resulting probe has a strong NIR absorption, sufficient stability, high photothermal conversion efficiency, and suitable photostability. In the study, RBCm-AuNSs were used to diagnose and treat mice carrying liver cancer after an *in vitro* feasibility assessment. It is stated that the photoacoustic imaging supported by RBCm-AuNSs can also reveal the location and size of tumors smaller than 2 mm in diameter. As can be seen, probes synthesized from gold nanostar are promising to assist in noninvasive diagnosis

and treatment of early stage cancers for translational and clinical applications.

Xia and co-workers [59] synthesized functional GNSs for targeted lung cancer therapy. MMPP polypeptides were used as targeting agents and IR-780 iodide was used both as a NIR fluorescence imaging agent and PTT/PDT agent. IR-780 iodide is an FDA-approved molecule for clinical applications and shows PTT and PDT effects in the presence of laser irradiation. However, the lack of tumor specificity and hydrophobic properties of photosensitizers limit their clinical application. In this system, GNS-coupled IR-780 molecules are said to exert a high therapeutic effect through synergistic action.

2D MnO₂ nanoplates are new nanomaterials, which have begun to attract attention as drug delivery systems, bioimaging, and theranostic agents. These nanoplates can easily be converted into Mn²⁺ ions in the tumor microenvironment

Fig. 7 Schematic illustration of RBCm-AuNSs for enhanced liver cancer photoacoustic diagnosis and photothermal therapy by Huang et al. [76]



(high levels of H_2O_2 and GSH and low pH) [77]. Leveraging this feature of MnO_2 nanosheets, GNS- MnO_2 nanoprobe have been synthesized by Liu et al. for magnetic resonance imaging-guided photothermal therapy of lung cancer. PTT studies have shown that nanoprobe kills lung cancer cells in a controlled manner, while not damaging normal lung epithelial cells [78].

Sardo et. al [79] coated GNS with two different polymers to deliver siRNAs inside cells with the advantages of gold nanoparticles, which can act as theranostic agents and radiotherapy enhancers through laser- induced hyperthermia. They determined that the siRNA complexes of all the coated GNS that they have tested were able to be internalized by MCF-7 cells to a larger extent than siRNA alone. Furthermore, they efficiently suppressed Luciferase expression within the cells without eliciting severe cytotoxicity.

Summary and outlook

GNSs is a versatile platform showing great promise for pre-treatment cancer diagnostics and cancer therapy, thanks to unique physicochemical properties such as surface plasmon resonance (SPR), light-thermal conversion ability, light scattering, and easy synthesis. However, due to the lack of tumor selectivity and its hydrophobic properties, GNS needs to be functionalized in various ways to be used in multifunctional diagnostic/treatment platforms.

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