Gold nanoparticles (AuNPs) are attractive photothermal agents for cancer therapy because they show efficient local heating upon excitation of surface plasmon oscillations. The strong absorption, efficient heat conversion, high photostability, inherent low toxicity and well-defined surface chemistry of AuNPs contribute to the growing interest in their photothermal therapy (PTT) applications. The facile tunability of gold nanostructures enables engineering of AuNPs for superior near-infrared photothermal efficacy and target selectivity, which guarantee efficient and deep tissue-penetrating PTT with mitigated concerns regarding side effects by nonspecific distributions. This article discusses the current research findings with representative near-infrared-active AuNPs, which include nanoshell, nanorod, nanocage, nanostar, nanopopcorn and nanoparticle assembly systems. AuNPs successfully demonstrate potential for use in PTT, but several hurdles to clinical applications remain, including long-term toxicity and a need for sophisticated control over biodistribution and clearance. Future research directions are discussed, especially regarding the clinical translation of AuNP photosensitizers.

**Keywords:** drug delivery • gold nanoparticle • medical imaging • nanomedicine • near-infrared • photothermal therapy • theragnostics

Hyperthermia is a medical treatment in which body tissues are exposed to a slightly higher temperature than normal conditions in order to damage and destroy cancer cells [1]. Tumor tissues have abnormally chaotic and sparse vascular structures, which results in difficulty in dissipating heat and thus being more sensitive to hyperthermia than healthy tissues [2]. Cancer cells can be selectively destroyed at temperatures between 40 and 44°C, where harmful effects such as DNA damage, protein denaturation and disruption of the cellular membranes occur and result in ablation of tumor tissues. Traditional hyperthermia treatments use hot water [3,4], microwaves [5,6], ultrasound (US) [7,8] and radiofrequency radiation [9,10] to deliver heat to tumors. While these methods efficiently heat the tumor tissues, they typically lack specificity for the tumor, which results in systemic toxicity as the result of the exposure of large volumes of normal tissues to hyperthermic temperature. Photothermal therapy (PTT) is a minimally invasive hyperthermic treatment method in which photon energy is converted to thermal energy in order to induce cancer hyperthermia.

Photosensitizers are typically coemployed with light irradiation for PTT. They absorb incident photons and relax the exited electron energy into heat through nonradiative decay channels. PTT can greatly improve the therapeutic efficiency of hyperthermia because heat can be selectively directed to tumor tissues by focused and directional control of the incident radiation and by the region-specific administration of the photosensitizers, which can result in localized heat transfer to the surrounding environment. Organic molecules, either endogenous pigments (e.g., oxyhemoglobin and melanin) [11] or exogenously prepared dyes (e.g., porphyrin...
Gold nanoshells

Gold nanoshells (GNSs) are composed of a dielectric core surrounded by a thin gold shell. Their SPR can be understood to be a result of plasmon hybridization between the inner shell and outer shell surfaces. The plasmon shift depends on the coupling strength and the energy difference between the plasmons on the inner and outer shells. As a result, the SPR wavelength of GNSs can be tuned from visible to NIR by adjusting the ratio of core radius to shell thickness [21]. The seed-mediated growth method is typically used to fabricate GNSs; in this process, small seed AuNPs are first attached to the dielectric core and subsequently grown to form a shell. Halas and coworkers pioneered use of GNSs and their patented invention has been clinically tested [22]. For example, Hirsch et al. reported GNS-mediated NIR PTT of tumors under magnetic resonance guidance [23]. They incubated human breast carcinoma cells with pegylated GNSs and demonstrated photothermal destruction of the cells after NIR laser irradiation ($\lambda = 820$ nm, $35$ W/cm$^2$; Figure 2). PEG was introduced to enhance colloidal stability, increase blood circulation times and increase the efficiency of tumor accumulation. Under magnetic resonance guidance, exposure of the GNS-treated tumor to NIR light caused it to reach the average maximal temperature within 4–6 min, which resulted in irreversible tissue damage and shrinkage of the tumor volume. Selective accumulation of GNSs in the target tumor tissue can be achieved by surface conjugation of targeting agents, such as antibodies and peptides that can recognize specific cell types. Loo et al. [24] and Fekrazad et al. [25] demonstrated that GNSs coated with anti-HER-2 antibodies such as Herceptin® (Genentech, CA, USA) can target breast cancer cells with high specificity. Liu et al. reported that GNSs functionalized with small peptides to target liver cancer cells, where the functionalized GNSs showed selective photothermal destruction of the targeted cancer cells [26]. GNSs can be further functionalized to load various cargoes, including anticancer drugs, SPIO NPs and perflurorocarbons. Wu et al. reported a study of doxorubicin (DOX)-loaded liposome/silica/GNSs [27]. DOX is one of the most common anticancer agents in clinical use. It can intercalate within DNA and inhibit the macromolecular biosynthesis that is critical for cancer cells to divide and grow. DOX-loaded liposomes were coated with a thin silica layer, then the gold shell was grown using a seed-mediated growth approach to fabricate GNSs that encapsulated the DOX-loaded liposomes. The DOX-loaded GNSs destroyed cancer cells with high therapeutic efficacy when irradiated with NIR laser.
light; this result suggests a synergistic effect because the GNSs activated both chemotherapy and PTT. You et al. investigated DOX-loaded hollow gold nanospheres (DOX@HAuNSs) and conjugated them with a peptide sequence that targets EphB4, a tyrosine kinase receptor that is often overexpressed on tumor cell membranes and angiogenic blood vessels [28]. NIR laser irradiation after treatment with targeted DOX@HAuNSs resulted in significantly suppressed tumor growth when compared with the control treatment with nontargeted DOX@HAuNSs or HAuNSs. Melancon et al. demonstrated investigated GNSs that encapsulated SPIO NPs and that were externally conjugated with C225 antibodies that target EGFR, reporting their effectiveness in selective magnetic resonance-guided PTT [29]. Ma et al. developed GNS-coated cholesteryl succinyl silane (CSS) nanomicelles loaded with DOX and SPIO (CDF–GNSs) for the multiple functions of MRI, magnetic target drug delivery, light-triggered drug release and PTT (Figure 3) [30]. CSS molecules can form self-closed spheres called micelles. Upon ultrasonication, CSSs in conjunction with DOX and SPIO NPs form nanomicelles due to the strong interactions between cholesterol groups, hydrophobic DOX and oleic acid-stabilized SPIO NPs. GNSs can be grown on the surface of the nanomicelles. Cancer cells incubated with CDF–GNSs showed significant cell mortality after exposure to both NIR light and a magnetic field; this mortality was attributed to the synergy between PTT and magnetic field-guided drug delivery. Ke et al. fabricated GNSs for bimodal US/MRI by incorporating SPIO and perfluorooctyl bromide into biodegradable polymer nanocapsules. Perfluorooctyl bromide is a chemically inactive and nontoxic compound, and can be used as a US contrast agent [31]. The resultant multicomponent GNSs exhibited bimodal US/MRI-guided PTT in mice to which human tumors had been xenografted. AuroShell™ (Nanospectra Bioscience, TX, USA) is also a GNS; it is currently being evaluated in a clinical study [32]. AuroShell is injected into the patient’s bloodstream and accumulates in tumors due to the enhanced permeability and retention effect. Blood vessels of tumor cells are typically leaky and poorly organized due to their active angiogenesis. Most tumor tissues therefore exhibit enhanced vascular permeability. Because tumor tissues usually lack effective lymphatic drainage, AuroShell can accumulate in tumors selectively. After AuroShell accumulates in the tumor, the area of interest is illuminated by a NIR laser. GNSs enable selective and precise thermal destruction of tumors while minimizing damage to healthy adjacent tissue.

Gold nanorods

Gold nanorods (GNRs) exhibit two plasmon resonances: one transverse and the other longitudinal. The transverse band is typically at λ = 520 nm; the longitudinal band appears within a wide range of visible and NIR wavelengths depending on the aspect ratio (length divided by width) of the nanorod [33]. As the aspect ratio increases, the longitudinal peak is red-shifted. Gans theory can explain the optical properties of GNRs; this theory is an extended version of Mie theory with some geometric factors [34]. The efficient NIR absorption by the longitudinal mode of GNRs is well suited for PTT and enables deep penetration into biological tissues. Huang et al. investigated in vitro NIR PPT using anti-EFGR-conjugated GNRs [35]. The GNRs bound specifically to the surfaces of malignant-type cells that overexpressed EGFRs on their cytoplasmic membranes. As a result, the GNRs were observed selectively in the malignant cells. The malignant cells were destroyed at a laser power of approximately half of that needed to kill nonmalignant cells (Figure 4). The group later demonstrated the feasibility of in vivo PTT using pegylated GNRs [36]; they observed a dramatic size reduction in human squamous carcinoma tumors treated with GNRs and PTT. Pissuwan et al. used antibody-conjugated GNRs and demonstrated targeted photothermal destruction of murine macrophage cells [37] and parasitic protozoans [38]. The latter work is one of the very few publications that report targeting of a live protozoan parasite. Choi et al. developed GNR-loaded functional nanocarriers (chitosan-conjugated, Pluronic-based nanocarriers) that efficiently accumulated in tumor by the enhanced permeability and retention effect and showed successful PTT [39]. An intravenous injection of this nanocarrier followed by NIR laser irradiation of the tumor resulted in apparently complete tumor resorption without damage to the surrounding tissue.
Table 1. Properties and biomedical applications of gold nanoparticles.

<table>
<thead>
<tr>
<th>Size (nm)</th>
<th>SPR peak (nm)</th>
<th>Surface molecules/cargoes</th>
<th>Target</th>
<th>Cell line/animal model</th>
<th>Biomedical applications</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>GNSs</td>
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<tr>
<td>~65</td>
<td>820</td>
<td>PEG</td>
<td>–</td>
<td>SKBR3 cells/CB17-1ldclsdclsdclscldsdclsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclscldsdclsd</td>
<td>PTT</td>
<td>[23]</td>
</tr>
<tr>
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<td>800</td>
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<td>SKBR3 cells</td>
<td>PTT</td>
<td>[24]</td>
</tr>
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<td>~110</td>
<td>820</td>
<td>PEG, anti-HER-2 nanobodics</td>
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<td>KB cells</td>
<td>PTT</td>
<td>[25]</td>
</tr>
<tr>
<td>~160</td>
<td>800</td>
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<td>BEL-7404</td>
<td>BEL-7404 cells</td>
<td>PTT</td>
<td>[26]</td>
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<tr>
<td>~240</td>
<td>810</td>
<td>DOX</td>
<td>–</td>
<td>SMMC-7721 cells</td>
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<td>[27]</td>
</tr>
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<td>EphB4</td>
<td>Hey cells/Swiss mice bearing Hey tumors</td>
<td>Drug delivery, PTT</td>
<td>[28]</td>
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<td>800</td>
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<td>EGFR</td>
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<td>PTT, MRI</td>
<td>[29]</td>
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<tr>
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<td>400 - 900</td>
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<td>HeLa cells</td>
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<td>[30]</td>
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<tr>
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<td>–</td>
<td>HT-1080 cells/Balb/c nude mouse implanted with HT-1080</td>
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<td></td>
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<tr>
<td>12/50 (width/length)</td>
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<td>EGFR</td>
<td>HOC 313, HSC-3 cells</td>
<td>PTT</td>
<td>[35]</td>
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<tr>
<td>12/50</td>
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<td>PEG</td>
<td>–</td>
<td>Hu/nu mice implanted with HSC-3 tumors</td>
<td>PTT</td>
<td>[36]</td>
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<td>Raw 264,7 murine macrophage cells</td>
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<td>[38]</td>
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<tr>
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<td>PEG</td>
<td>–</td>
<td>Nude mice bearing MDA-MB-435 tumors</td>
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<td>[47]</td>
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<td>OSCC15, MDA-MB-231, MCF7 cells</td>
<td>OCT, PTT</td>
<td>[49]</td>
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CT: Computed tomography; CTAB: Cetyltrimethylammonium bromide; DOX: Doxorubicin; EGFR: EGF receptor; GNC: Gold nanocage; GNP: Gold nanopopcorn; GNR: Gold nanorod; GNS: Gold nanoshell; GNST: Gold nanostar; GV: Gold vesicle; HB: Hypocrellin B; NP: Nanoparticle; OCT: Optical coherence tomography; PA: Photoacoustic; PFOB: Perfluorooctyl bromide; PNP: Poly-N-isopropylacrylamide; PSS: Poly(sodium-p-styrenesulfonate); PT-OCT: Photothermal optical coherence tomography; PTT: Photothermal therapy; SAN: ‘Smart’ gold nanoparticle; SPIO: Superparamagnetic iron oxide; SPR: Surface plasmon resonance; SWCNT: Single-wall carbon nanotube; TCAp: Calcium phosphate; TVT: Transmissible venereal tumor; US: Ultrasound.
<table>
<thead>
<tr>
<th>Size (nm)</th>
<th>SPR peak (nm)</th>
<th>Surface molecules/cargoes</th>
<th>Target</th>
<th>Cell line/animal model</th>
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<td>HeLa cells</td>
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<td>[69]</td>
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<td>4 [80], 10</td>
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<td>pH-responsive molecules, DOX-conjugated pH-responsive molecules, Raman-active probes, SAN–liposome hybrids</td>
<td>−</td>
<td>B16F10, HeLa cells/nude mice bearing B16F10 tumors</td>
<td>Drug delivery [76], Raman imaging [77], PT-OCT [78], PA imaging, PTT [79]</td>
<td>[75–80]</td>
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CT: Computed tomography; CTAB: Cetyltrimethylammonium bromide; DOX: Doxorubicin; EGF: EGF receptor; GNC: Gold nanocage; GNP: Gold nanopopcorn; GNR: Gold nanorod; GNS: Gold nanoshell; GNST: Gold nanostar; GV: Gold vesicle; HB: Hypocrellin B; NP: Nanoparticle; OCT: Optical coherence tomography; PA: Photoacoustic; PFOB: Perfluorooctyl bromide; PNIPAM: Poly(N-isopropylacrylamide); PMAA: Prostate-specific membrane antigen; PSS: Polysodium-p-styrenesulfonate; PT-OCT: Photothermal optical coherence tomography; PTT: Photothermal therapy; SAN: ‘Smart’ gold nanoparticle; SPIO: Superparamagnetic iron oxide; SPR: Surface plasmon resonance; SWCNT: Single-wall carbon nanotube; TCaP: Calcium phosphate; TVT: Transmissible venereal tumor; US: Ultrasound.
For GNRs to be useful in PTT, they must be functionalized. GNRs are usually synthesized with cetyltrimethylammonium bromide (CTAB), which can be quite toxic and does not provide functionalities for surface modifications. Several surface functionalization strategies have been developed for GNRs in order to increase their capability for biological applications [40]. In most cases, thiolated molecules were introduced in order to replace CTAB by place-exchange reactions using the strong gold–sulfur affinity. In particular, GNRs that were surface-modified with thiolated PEG showed small, nonspecific adsorptions of biomolecules, and as a result, their in vivo circulation times and accumulation in tumors were greatly improved [41]. Another strategy is to construct a mesoporous silica shell around the GNR. Mesoporous silica shells possess several advantages: they can be used as reservoirs for hydrophobic drugs for drug delivery applications, and can form a protective layer against laser-induced photothermal reshaping of GNRs because heat dissipates faster into the silica shells than into CTAB layers [42]. In addition, functional moieties can be easily introduced onto the silica shells by silane coupling reactions [43]. Layer-by-layer polyelectrolyte assembly by sequential electrostatic adsorption can be used to functionalize GNRs. Qiu et al. found that multilayer polyelectrolyte-coated GNRs can reduce the toxicity and increase cellular uptake compared with the case of CTAB-coated GNRs [44]. The multilayered polyelectrolyte-coated GNRs were synthesized by sequentially coating the CTAB-coated GNRs with negatively charged poly(sodium-p-styrenesulfonate) and positively charged poly(diallyldimethylammonium chloride). A single layer of electrostatically self-assembled, negatively charged polyacrylic acid on CTAB-coated GNRs was also reported by Kirui et al. [45]. The carboxylic group of polyacrylic acid allowed consistent biomolecule couplings by standard carboxylic acid–amine conjugations.

GNRs provide a versatile platform that can integrate multiple therapeutic modalities. Chemo-PPT using DOX–GNR complexes was demonstrated by Xu et al. [46]. They synthesized hyaluronic acid (HA)-conjugated nanographene oxide (NGO)-enwrapped GNRs (NGO–HA-AuNRs), where AuNR is another acronym for gold nanorod representing the same as GNR. HA modification improved the colloidal stability of NGO-AuNRs and targeted hepatoma cells. The NGO–HA-AuNRs was applied to load DOX, and they exhibited both targeting to hepatoma Huh-7 cells and light-triggered drug release. Combination therapy by NGO–HA-AuNR–DOX showed 1.5–4-times higher cell mortality than chemotherapy or PTT alone (Figure 5). GNRs have also been successfully adopted...
in bioimaging techniques for cancer diagnoses, such as computed tomography, photoacoustic (PA) imaging and optical coherence tomography (OCT). Von Maltzahn et al. showed that the intrinsic x-ray scattering properties of GNRs can be used to guide PTT by computed tomography imaging and so increase therapeutic efficacy [47]. Yeager et al. used silica GNRs as a PA contrast and PTT agent [48]. The GNRs were endocytosed by phagocytically active macrophages within atherosclerotic regions and generated US for PA imaging upon laser heating; GNR-assisted PTT of atherosclerotic plaques was also demonstrated. Black et al. synthesized polydopamine (PD)-coated GNRs [49]. Anti-EGFR antibodies were conjugated to the PD-coated GNRs, and the anti-EGFR-conjugated, PD-coated GNRs were successfully used for targeted PTT and OCT.

**Gold nanocages**

Sun et al. developed a novel class of noble metal nanostructures: gold nanocages (GNCs) [50]. GNCs have a hollow structure with porous walls and can be synthesized using a galvanic replacement reaction between a sacrificing template of silver nanocubes and a gold precursor (chloroauric acid). By adjusting the amount of gold precursor, the SPR peak of GNCs can be controlled in the range of 600 nm ≤ λ ≤ 1200 nm [51]. Their tunability in SPR, hollow interiors and porous walls make GNCs suitable for various biological applications, including PTT and drug delivery. Chen et al. demonstrated the photothermal effect of GNCs on SK-BR-3 breast cancer cells [52]. GNCs conjugated with anti-HER-2 antibodies showed selective photothermal destruction of the breast cancer cells. To optimize treatment parameters (e.g., dosage of GNCs, power density and exposure time of the laser) for in vivo study, Au et al. quantified both the number of GNCs immobilized per cell and the photothermal effect as a function of the GNC concentration [53]. Chen et al. later investigated in vivo PTT using pegylated GNCs [54]. U87MG-wtEFGFR tumor-bearing mice were injected intravenously with pegylated GNCs or saline, and the tumors were subjected to PTT under exposure to NIR laser after 72 h. The surface temperature of the tumor increased rapidly to 50°C within 1 min in the GNC-injected mice, but showed no noticeable change in the saline-injected mice (Figure 6A). The metabolic change in tumors before and after the laser treatment was evaluated by 18F-fluorodeoxyglucose PET (Figure 6B). Irreversible damage to the tumor cells in mice injected with GNCs was confirmed by histological examinations (Figure 6C & 6D). The authors have further demonstrated that GNCs could be used as a PA contrast agent for surgical and PTT guidance; when conjugated with the ligand of melanocortin type-1 receptor, GNCs actively targeted tumors and showed approximately 300% increased PA signals. GNCs have also been shown to be effective for photothermal/photodynamic cancer therapy in vitro. Khlebtsov et al. functionalized silica-coated GNCs with a photodynamic sensitizer, Yb-2,4-dimethoxyhematoporphyrin [55]. The nanocomposite generated singlet oxygen, and at the same time produced heat under laser irradiation. It also exhibited NIR luminescence (900 nm ≤ λ ≤ 1060 nm) that originated from Yb3+ ions in the Yb-2,4-dimethoxyhematoporphyrin. Gao et al. introduced a photosensitizer, hypocrellin B, to lipid-coated GNCs [56]. When HeLa cells were pre-incubated with the nanocomplex and irradiated by a 790-nm femtosecond pulse laser, the GNCs converted light into heat and hypocrellin B generated reactive oxygen species simultaneously. Synergistic anticancer efficiency was suggested by the combination of photodynamic therapy and PTT. Khan et al. modified GNC-decorated single-wall carbon nanotubes (SWCNTs) with A9 RNA aptamers, which are specific to human prostate cancer cells [57]. The aptamer-conjugated GNC–SWCNT hybrids showed highly selective photothermal destruction of prostate cancer cells. Controlled delivery of the drug with GNCs was also

**Figure 2. Localized photothermal destruction of cells as determined by calcein acetoxymethyl ester and fluorescein dextran.** (A & C) Cells irradiated without nanoshells maintained both viability and membrane integrity on laser irradiation. (B & D) Cells irradiated with nanocells showed photothermal destruction within the laser spot. The 820 nm laser was irradiated at 35 W/cm² for 7 min.

AM: Acetoxymethyl ester.

Figure 3. Cholesteryl succinyl silane–gold nanoshell. CSS–gold nanoshells consist of three functional parts: DOX as a chemotherapeutic agent; Fe\textsubscript{3}O\textsubscript{4} NPs for both MRI and magnetic-targeted drug delivery; and a gold nanoshell used for both NIR light-triggered drug release and photothermal therapy. CDF nanomicelles: Cholesteryl succinyl silane nanomicelles loaded with DOX and Fe\textsubscript{3}O\textsubscript{4} NPs; CSS: Cholesteryl succinyl silane; DOX: Doxorubicin; NIR: Near-infrared; NP: Nanoparticle.


demonstrated. Shi et al. reported a smart therapeutic nanoplatform based on GNCs with calcium phosphate (CaP)-coated Fe\textsubscript{3}O\textsubscript{4} NPs (Fe\textsubscript{3}O\textsubscript{4}@CaP-capped GNCs; Figure 7) [58]. GNCs were functionalized with bisphosphonates that can bind to CaP on Fe\textsubscript{3}O\textsubscript{4} NPs. The bisphosphonate-functionalized GNCs were applied to load DOX, and Fe\textsubscript{3}O\textsubscript{4}@CaP capped the pores of the GNCs. The Fe\textsubscript{3}O\textsubscript{4}@CaP-capped, DOX-loaded GNCs showed pH-triggered drug release because CaP can be dissolved in the acidic cellular environment. GNCs have been used in targeting and show a synergistic effect by combining chemotherapy and PTT. Yang et al. developed a NIR stimulus-controlled drug delivery system based on GNCs with mesoporous silica shells [59]. The GNCs with mesoporous silica shells was loaded with DOX and functionalized with thermally responsive poly(N-isopropylacrylamide) (PNIPAM) on the surface. PNIPAM can convert its hydrophilicity and hydrophobicity at a critical temperature (~32°C); when temperatures exceeds this threshold, water molecules are dramatically expelled from PNIPAM, which therefore shrinks significantly. Upon laser irradiation, GNCs can effectively convert NIR light to heat and induce the collapse of PNIPAM. As a result, mesoporous silica shells open their pores to the surroundings and thus release the entrapped DOX.

**Gold nanostars & gold nanopopcorns**

Gold nanostars (GNSTs) and gold nanopopcorns (GNPs) are highly anisotropic NPs that are composed of a small core and a number of sharp tips. The optical properties of these NPs depend strongly on the sizes of the protruding tips and exhibit high absorption cross-sections in the NIR region as a result of hybridizations of the plasmons of the core and the tips of NPs [60]. Several studies have reported high-yield
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**Figure 4. Selective photothermal therapy of cancer cells incubated with EGFR-conjugated gold nanorods.**

Circles: position of laser spots on the samples. At 80 mW (10 W/cm²), the HSC and HOC malignant cells are obviously damaged, but the HaCat normal cells are not noticeably damaged. The HaCat normal cells begin to be damaged at 120 mW (15 W/cm²) and are obviously damaged at 160 mW (20 W/cm²).


synthesis of GNSTs, typically by using seed-mediated synthesis and growth with or without the use of surfactants [61–66] or by simple seedless synthesis using 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES), in which HEPES served as both the reducing and shape-directing agent [67,68]. GNSTs conjugated to drugs have been applied in tumor treatment. Van De Broek et al. demonstrated the conjugation of GNSTs to anti-HER-2 nanobodies for target-specific photothermal cancer destruction [64]. HER-2-positive SKOV3 cells incubated with the anti-HER-2 targeting GNSTs were destroyed after 5 min of 660-nm continuous wave (cw) laser treatment at 38 W/cm² (Figure 8). Yuan et al. demonstrated the photothermal ablation of SKBR3 breast cancer cells incubated with bare GNSTs within 5 min of irradiation (980-nm cw laser, 15 W/cm²) [65]. When pegylated GNSTs were systemically administered to mice and accumulated for
Figure 5. Cytotoxicity of hepatoma Huh-7 cells treated with different methods. (A) Cytotoxicity of cells incubated with NGO–HA, NGO–AuNRs and NGO–HA–AuNRs with/without laser irradiation. (B) Cytotoxicity of cells incubated with DOX, NGO–HA–DOX and NGO–HA–AuNR–DOX with/without laser irradiation. 

AuNR: Gold nanorod; DOX: Doxorubicin; HA: Hyaluronic acid; NGO: Nanographene oxide; NIR: Near-infrared.


2 days, extravasation of GNSTs was demonstrated and localized photothermal ablation was reported at the dorsal window chamber within 10 min of irradiation (785 nm cw laser, 1.1 W/cm²). Yuan et al. also reported enhanced intracellular delivery by TAT peptide-functionalized GNSTs (TAT being one of the most studied cell-penetrating peptides) and efficient in vitro PTT of cancer cells [66]. After 4 h incubation of TAT–GNSTs with BT549 breast cancer cells, a distinct ablation was observed under irradiation with an NIR laser (≥0.2 W/cm²); this irradiation power was lower than previously reported values obtained using pulsed lasers. Chen et al. conjugated GNSTs with cyclic RGD and an anticancer drug (DOX) to show the synergistic effects of PTT and chemotherapy [68]. Under 785-nm cw laser irradiation for 10 min (1.0 W/cm²), anticancer activity of GNST–cyclic RGD–DOX on MDA-MB-231 breast cancer cells (high αvβ3 receptor expression) was noted in >90% of cells, which was significantly higher than that of GNST or DOX alone, or of nontargeted GNST–DOX at the same dose level. GNPs also offer unique NIR-absorbing plasmon properties and efficient conversion of photon energy into heat. GNPs are typically synthesized using a seed-mediated growth approach. Small (<5 nm), spherical, reasonably uniform seed AuNPs were obtained using trisodium citrate and sodium borohydride, then sharp tip structures were grown using ascorbic acid as a weak reductant and CTAB as a shape templating agent. Lu et al. developed a targeted photothermal therapeutic agent by modifying the surface of GNPs with anti-prostate-specific membrane antigen (PSMA) antibodies [69]. LNCaP human prostate cancer cells were incubated with the anti-prostate-specific membrane antigen GNPs and demonstrated significant mortality after 30 min of irradiation (785-nm cw laser, 12.5 W/cm²; Figure 9). For synergistic PTT, Beqa et al. exploited SWCNTs to enhance the photothermal efficacy of GNPs [70]. GNPs were conjugated to the surface of SWCNTs using a chemical anchor, para-aminothiophenol, and were modified with SKBR3 breast cancer cell-specific S6 aptamers. After incubation of the SKBR3–GNP–SWCNT hybrid nanomaterial with SKBR3 cells for 24 h, photodestruction of the SKBR3 breast cancer cells was observed upon exposure to 785-nm light with 1.5 W/cm² power for 10 min.

AuNP assembly systems

Gold nanospheres can have advantages in practical PTT applications over anisotropic nanostructures such as nanoshells, nanorods, nanostars and nanopopcorns because the synthesis of nanospheres is generally simple and produces uniform-sized particles easily, and is suitable for large-scale production. Nanospheres show high stability under high-power laser irradiation because of their intrinsic thermodynamic stability. They can be prepared to a size that is smaller than anisotropic gold nanostructures, which are typically >50 nm; this small size can yield efficient endocytosis into cancerous cells [71,72]. Small nanospheres (<6 nm)
can potentially be excreted through renal pathways and thereby alleviate the potential clearance problems when used clinically [73]. However, their plasmon resonance peaks are typically restricted to the visible region, in which the photons have low tissue penetration depths and are not efficient for in vivo PTT applications. To move the SPR mode to the NIR region, coupled plasmon modes of nanospheres can be exploited by using aggregated or assembled systems. Huang et al. reported that 30-nm gold nanospheres conjugated with anti-EGFR could be assembled on cell membranes that overexpressed EGFR at high concentrations [74]. The surface plasmon peak of the assembled nanospheres was red-shifted when compared with the initial state. The targeting NPs selectively destroyed cancer cells under NIR laser irradiation at only 5% of the power density required to destroy cells treated with no NPs. Appropriate functionalization of GNPs can be used to increase their effectiveness at both entering cells and remaining within them. Nam et al. reported a pH-induced aggregation system using ‘smart’ AuNPs (SANs) that were designed to selectively form aggregates under mildly acidic conditions, such as the intracellular environment or in a tumor microenvironment [75]. SANs consist of a 10-nm gold nanosphere and pH-sensitive surface molecules that contain a hydrolysis-susceptible citraconic amide unit and a dithiol group for surface anchoring. The citraconic amide bond is stable under neutral or basic conditions, but tends to hydrolyze abruptly at a pH <7. The SAN surfaces were engineered to possess both positive and negative charges under acidic conditions; these charges induce

Figure 6. In vivo photothermal therapy using gold nanocages. (A) Plots of average temperatures within irradiated area as a function of irradiation time. (B) Ratios of laser-treated tumor (Rt tumor) to nontreated tumor (Lt tumor) 18F-fluorodeoxyglucose SUVs (p < 0.001). (C) Representative histology image of tumor tissue from a gold nanocage-injected mouse with irradiation. (D) The corresponding magnified image of the area in the black box in (C). Tumors from mice treated with nanocages and laser irradiation showed distinctive characteristics of cellular damage, such as abundant pyknosis (colored arrow), karyorrhexis (open arrow), karyolysis (arrowhead) and interstitial edema (asterisk). SUV: Standardized uptake value.

rapid aggregation between the NPs by electrostatic attraction. The pH-responsive aggregation shifts the absorption of SANs to NIR due to coupling of the plasmon modes among the NPs. The SANs showed highly specific accumulation in cancer cells due to the enhanced phagocytic activity of cancer cells and because exocytosis was efficiently blocked due to the SANs forming aggregates inside the cells. The aggregates formed inside of cells can absorb deep tissue-penetrating NIR light, and this has been well demonstrated for efficient PTT. As a result, SANs showed selective and efficient destruction of cancer cells at a relatively low threshold of laser power ($6.5 \text{ W/cm}^2$), and the cell mortality linearly increased with the irradiation power density. SAN-based combination therapy was further demonstrated by using the carbodiimide coupling reaction in order to covalently conjugate the anticancer drug DOX to the terminals of surface molecules [76]. The SAN–DOX conjugate (SANDC) was designed to release the DOX payload by pH-triggered linker cleavage under the mildly acidic condition within tumors, and to simultaneously form aggregates of AuNPs, which can be exploited for PTT (Figure 10). SANDCs demonstrated colocalizations of the DOX and AuNP aggregates; significant proportions of both species were found at the cell nuclei. The tethered DOX may have induced the translocation of SANDCs to the nuclei. The combination of PTT and chemotherapy with SANDCs showed a significant synergistic factor of approximately 7, possibly due to spatiotemporal co-occurrence of DOX and AuNPs. The therapeutic effect at the in vivo organ level, as well as at the cell level, of the SANDCs was investigated using nu/nu nude mice bearing B16F10 melanoma cells grafted onto the flank. SANs and SANDCs showed significantly high accumulations in tumors of 10.9 and 5.0% injected dose per gram of tumor, respectively, compared with the control AuNPs, which did not have the pH-induced aggregation function. SANDCs displayed the largest tumor suppression, reducing the final tumor size to half the size of that attained using SANs alone or using a physical mixture of SAN and DOX treatment, and 5% as large as tumors in the control cases (AuNP alone or saline blank treatment). The effects of theragnostic SANs were demonstrated by surface codecoration with the pH-responsive ligand and a Raman-active probe [77]. Under mildly acidic conditions, the theragnostic SANs formed aggregates due to the pH-responsive ligands, and this aggregation shifted the absorption to the NIR region, which is optimal for deep tissue penetration. At the same time, this aggregation provided hot spots for surface-enhanced Raman scattering of the codecorated Raman-active probes, with an enhancing factor of $1.3 \times 10^4$. The coupled plasmon resonances of the pH-induced aggregations simultaneously provided hot-spots for the surface-enhanced Raman scattering probe and shifted the absorption to NIR; this shift was successfully exploited using a ‘turn-on’ theragnostic agent for simultaneous Raman imaging/diagnosis and low-threshold PTT. The theragnostic SANs were cancer specific because they aggregated rapidly and accumulated selectively in...

Figure 7. Fe$_3$O$_4$ @calcium phosphate-capped gold nanocage.
DOX: Doxorubicin; NIR: Near-infrared
Adapted from [58] with permission from the Royal Society of Chemistry.
cancerous cells. Consequently, both Raman imaging and photothermal efficacy were turned on in a cancerous local environment. This result demonstrates that theragnostic SANs can be used to target tumor areas and to focus on areas that require laser-induced photothermal destruction. SANs can also be used to detect cancer cells. Xiao et al. demonstrated the feasibility of combining the use of SANs and photothermal OCT (PT-OCT) for this purpose [78]. PT-OCT successfully detected the pH-induced aggregations by combining an OCT light source and a laser with \( \lambda = 660 \) nm for photothermal excitation. Optical detection of the pH-induced aggregation was tested; an increase in optical path length variation was measured under mildly acidic conditions, but the change was small under neutral conditions. The detection of cancer cells was tested with cultured cell samples. HeLa and fibroblast cells, as cancer and normal cells, respectively, were measured using PT-OCT. An elevated signal was detected with the HeLa cells, but the change was small with the fibroblast cells. Although SANs and their derivatives have demonstrated their capability for imaging and therapy, their significant clearance by the reticuloendothelial system (RES; e.g., liver and spleen) has severely limited their full exploitation in clinical translations. Surface coating with ‘stealth’ polymers such as PEG is often used to minimize nonspecific recognition and clearance by the RES organs; however, some NP systems, including SANs, do not allow such surface fabrications because they may alter the NP surface properties and thereby cause undesired changes in their physicochemical properties. Nam et al. reported a SANs-in-liposome hybrid nanostructure by encapsulating SANs in a PEG-grafted liposomal vehicle, in which the PEG-grafted liposome acts as a nonassociative surface passivation layer that provided an anti-fouling coating for encapsulated SANs [79]. The SANs-in-liposome hybrid nanostructure effectively combined the pH-responsive assembly and surface plasmon property changes of the SANs with the enhanced systemic circulation and tumor accumulation of the PEG-grafted liposomes. The hybrid consisted of PEG-grafted, pH-responsive liposome and a number of encapsulated SANs. SANs encapsulated in the liposome retained their initial surface properties and showed characteristic pH-responsive spectral red-shifts upon exposure to mildly acidic conditions. Transmission electron microscopy measurement confirmed the formation of AuNP aggregates inside the liposome. The liposomal passivation layer ensured minimum nonspecific interactions with the cells in vitro and largely reduced the uptake of encapsulated SANs by RES organs in vivo. As a result, 1.1–2.5-times increased accumulation of SANs in tumors was achieved, and this was accompanied by prolonged blood circulation and significantly decreased uptake. The hybrid effectively enhanced systemic circulation of payload SANs, which resulted in up to 2.5-times increased tumor accumulation compared with the case of pristine SANs. The development of a new protocol to synthesize such small SANs was necessary for this, because the method that is used to prepare SANs of >10 nm could not be applied to small SANs. Hwang et al. used a one-phase synthesis method to develop pH-responsive SANs with hydrodynamic (HD) size <6 nm [80]. These small SANs responded well to pH changes and formed aggregates in mildly acidic conditions, such as those of intratumoral or intracellular environments. The pH-responsive formation of aggregates caused the appearance of coupled plasmon modes that shifted the SPR to NIR; this shift was exploited for selective PTT. B16F10 mouse melanoma cells were coincubated with the small SANs; the photothermal effect was demonstrated at a laser power <20 W/cm\(^2\), and cell mortality increased linearly with irradiation power density. Small SANs could be very promising for clinical trials; effective tumor accumulation can be achieved due to the enhanced retention after the huge size increase by aggregation, whereas most untargeted NPs can be rapidly cleared from the body through renal pathways, thereby alleviating potential toxic side effects.

Recently, He et al. synthesized gold vesicles (GVs) composed of a monolayer of assembled AuNPs [81].
Self-assembly was triggered by adding water to a tetrahydrofuran solution of amphiphilic polymer-capped small gold nanospheres. The addition of water collapsed the hydrophobic part of the polymer to minimize the overall free energy of the system, thereby causing the polymer to assemble into large vesicles. The resulting GVs showed strong absorbance in the NIR region as a result of the plasmonic couplings among closely assembled AuNPs. A GV loaded with the photosensitizer Ce6 (GV–Ce6) was developed to improve the therapeutic efficacy of NIR fluorescence/PA imaging-guided synergistic photothermal/photodynamic therapy [82]. The efficient loading of Ce6 into GVs significantly increased the accumulation of Ce6 in cancer cells, and the encapsulated Ce6 was released upon laser irradiation. Tumor tissues treated with GV–Ce6 were visualized by the fluorescence and PA signal, and were confirmed to have been destroyed by laser illumination (Figure 11). Huang et al. later investigated biodegradable GVs composed of biodegradable copolymer poly(ethylene)-b-poly(ε-carprolactone)-tethered gold nanospheres for combined PA imaging and PTT [83]. Biodegradable GVs showed strong NIR absorption induced by the plasmon coupling, high photothermal conversion efficiency for simultaneous thermal/PA imaging and enhanced PTT with improved clearance due to the dissociation of particles after the therapy/imaging.

NP assembly systems are less sensitive to thermal degradation than anisotropic NPs and are therefore advantageous for use in PTT. One of the challenges in applying conventional anisotropic metal NPs for PTT is photothermal reshaping, which can make the NPs eliminate their sensitivity to laser excitation. For example, NIR pulsed laser light is typically used to excite the longitudinal surface plasmons of GNRs, but laser excitation often leads to the reshaping of GNRs into more spherical particles and a consequent disappearance of the longitudinal plasmon. Nam et al. reported a unique photothermal response of SAN aggregates in a comparative study with GNRs [84]. Upon laser excitation, the SAN aggregates showed spectral red-shift and retained their absorbing power in the NIR region; therefore, they retained their photothermal effect. By contrast, GNRs showed abrupt spectral blue-shift and loss of absorbing power in the NIR, and therefore lost their photothermal effect. Collective plasmon modes from NP assembly systems can preserve the photothermal effect at the continued excitation and showed dramatically higher temperature increases than anisotropic NPs. Considering the high temperatures required for transient and local heating for the efficient PTT agents, the thermal robustness of assembly systems is important for effective, long-term, stable photothermal imaging probes and/or PTT agents.

**Conclusion & future perspective:**

**AuNP-mediated PTT**

PTT can be a minimally invasive and highly efficient cancer treatment method that uses appropriate photosensitizers that can efficiently absorb incident photons in order to generate sufficient local heat. AuNPs represent a novel class of PTT photosensitizers with large absorption cross-sections [16] and are capable of efficient heat conversion due to the excitation of their surface plasmon oscillations [17]. Their easy tunability enables the development of unique gold nanostructures with superior NIR photothermal efficacy and target selectivity; these characteristics guarantee highly efficient deep tissue-penetrating PTT with reduced concerns regarding the side effects typically caused by nonspecific distributions of PTT agents in normal tissues. A photosensitizer based on single particles has been developed by using anisotropic gold nanostructures, such as nanoshells, nanorods, nanocages, nanostars and nanopopcorns, all of which have SPRs in the NIR region due to structure-directed or multiple surface plasmon modes. Spherical AuNPs typically show SPR characteristics in the visible wavelength regions, but these NPs can be engineered as NIR photosensitizers by using aggregation/assembly systems in order to tailor the SPR to the NIR region. Such AuNP-based photosensitizers have demonstrated efficient PTT both in vitro and in vivo. Recent advances have also led to multifunctional AuNPs that are not only capable of PTT, but also other functions, such as the delivery of anticancer drugs for combination therapy and as contrast agents for theragnosis.

A multifunctional system that integrates multiple therapeutics/diagnostics into a single formulation has potential as a ‘magic bullet’ with possible applications in a wide range of diseases.
Figure 10. Mechanism of the ‘smart’ gold nanoparticle-doxorubicin conjugate. SANDCs consist of SANs and covalently conjugated DOX. The SANDC is designed to release DOX by pH-triggered linker cleavage under the mildly acidic conditions in the tumor. Simultaneously, the SANDC is designed to convert the surface charge from negative to a mixture of negative and positive charges, which induces rapid aggregation among the nanoparticles due to electrostatic interactions. This spatiotemporally concerted release from SANDCs is exploited for chemotherapy and photothermal combination cancer therapies.

DOX: Doxorubicin; SAN: ‘Smart’ gold nanoparticle; SANDC: ‘Smart’ gold nanoparticle-doxorubicin conjugate.

Adapted with permission from [76] (copyright © [2013] American Chemical Society).

Since the Nanotechnology Characterization Laboratory (NCL) was founded in 2004, hundreds of nanomaterials have been tested for use in clinical cancer therapy [85]. The first AuNP-mediated cancer therapy to have reached early-phase clinical trials is CYT-6091, which consists of 27-nm AuNPs bound with thiolated PEG and TNF-α. A Phase 1 study of CYT-6091 in 29 patients was initiated in 2005. An efficacy study in combination with chemotherapy is also planned [86]. A clinical study of AuroShell is currently recruiting participants [32]. However, only a few nanomaterials have been evaluated in clinical studies and many obstacles to clinical translation remain. Sophisticated control over the biodistribution/clearance of these NPs and resolving long-term toxicity issues are prerequisites for the practical application of AuNPs. The in vivo fate
of NPs is governed by diverse physicochemical properties, such as HD size, surface charge, \textit{in vivo} stability and specific chemical interactions with biomolecules; because of the inherent complexity of this fate, full control over the biodistribution of NPs is a difficult task. In addition, NPs can broadly distribute themselves in many normal tissues by penetrating size-dependent organ barriers and can be easily trapped in the organs of the RES system after systemic administrations; this trapping raises significant concerns regarding the toxicity of AuNPs to these off-target tissues. Although gold is generally considered to be biocompatible and nontoxic, the unique properties of AuNPs (e.g., their high surface-to-volume ratio and large number of surface dangling bonds) can significantly increase their chemical/biological activity, thereby potentially causing harmful effects, such as the generation of reactive oxygen species. NP surface molecules introduced for colloidal stability or chemical functionalization also represent possible toxicity problems. The long-term toxicity of AuNPs due to nonspecific accumulation in untreated organs is relatively poorly understood and further comprehensive assessments are required because of the physicochemical properties of NPs.

Anisotropic gold nanostructures (such as GNSs, GNCs, GNRs, GNSTs and GNPs) can effectively absorb NIR light, but they may undergo photothermal reshaping, which may prevent their continuous photothermal effect. They are larger than approximately 50 nm, which is above the size limit (∼5 nm) for efficient renal clearance. SANs can have a relatively small size (<6-nm HD size), which is favorable for efficient renal clearance.

### Executive summary

- Gold nanoparticles (AuNPs) represent a novel class of photothermal therapy (PTT) photosensitizer with large absorption cross-sections and efficient heat conversions at the excitation of their surface plasmon oscillations.
- The surface plasmon resonance wavelength of gold nanoshells can be tuned to the near-infrared (NIR) region, which is well suited for PTT, and can be further functionalized to load various cargoes, including anticancer drugs, superparamagnetic iron oxide nanoparticles (NPs) and perfluorocarbons.
- The efficient NIR absorption by the longitudinal mode of gold nanorods is exploited for PTT; they provide a versatile platform that can integrate multiple therapeutic modalities.
- Gold nanocages are suitable for various biological applications, including PTT and drug delivery, due to their tunability of surface plasmon resonance, hollow interiors and porous walls.
- Anisotropic NPs, such as gold nanostars and gold nanopopcorns, exhibit high absorption cross-sections in the NIR region, which make them efficient photothermal agents.
- The coupled plasmon modes of nanospheres can be exploited using aggregated or assembled systems; these AuNP-based assembly systems have proven to be efficient for PTT both \textit{in vitro} and \textit{in vivo}.
- Sophisticated control over the biodistribution/clearance of these NPs and resolving the long-term toxicity issues are prerequisites for the practical application of AuNPs.
- An ideal AuNP photosensitizer for clinical applications should have high photothermal efficacies in the NIR region and should show selective accumulation in the target sites. The NPs should also be cleared rapidly from the body after their mission.
excretion, and they can effectively utilize NIR light after aggregating in response to pH. GVs can be bio-degradable and can effectively absorb a broad range of NIR wavelengths. However, their size is approximately 20 nm; this size limits effective renal clearance of GVs after therapy. An ideal AuNP photosensitizer for clinical applications should have high photothermal efficacy in the NIR region in order to achieve complete ablation of the tumor tissues. To alleviate possible toxicity concerns, the AuNPs should show selective accumulation in target sites with minimal nonspecific distribution. They should also be rapidly cleared from the body after their mission in order to prevent redistribution into off-target sites. The development of the sophisticated fabrication of AuNPs in order to meet these requirements is being actively pursued.

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