Gold-based Inorganic Nanohybrids for Nanomedicine Applications

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Abstract

Noble metal Au nanoparticles have attracted extensive interests in the past decades, due to their size and morphology dependent localized surface plasmon resonances. Their unique optical property, high chemical stability, good biocompatibility, and easy functionalization make them promising candidates for a variety of biomedical applications, including bioimaging, biosensing, and cancer therapy. With the intention of enhancing their optical response in the near infrared window and endowing them with additional magnetic properties, Au nanoparticles have been integrated with other functional nanomaterials that possess complementary attributes, such as copper chalcogenides and magnetic metal oxides. The as constructed hybrid nanostructures are expected to exhibit unconventional properties compared to their separate building units, due to nanoscale interactions between materials with different physicochemical properties, thus broadening the application scope and enhancing the overall performance of the hybrid nanostructures. In this review, we summarize some recent progresses in the design and synthesis of noble metal Au-based hybrid inorganic nanostructures for nanomedicine applications, and the potential and challenges for their clinical translations.

Key words: Au nanoparticles; hybrid nanostructures; localized surface plasmon resonances; nanomedicine; theranostics

Introduction

Although huge economic and scientific efforts have been invested in cancer research worldwide, more than 10 million new cancer cases are diagnosed each year, with death toll continues to rise [1-4]. Biomedical nanotechnology, including molecular diagnostic and nanotherapeutics that provide new options for clinical treatment, has recently been shown as a very promising technology to improve cancer patients’ treatment outcomes and reduce the socioeconomic burden. Potential clinical applications of nanotechnology can be categorized depending on its usage on the body as either outside (such as “point-of-care” testing) or inside (such as diagnostics and targeted drug delivery). When focusing on their clinical application inside the body, it is highly desirable to develop strategies that enable real-time tracking of the therapeutic response during the treatment, in order to avoid insufficient treatment or over-dosing side effect. In recent years, theranostic strategies based on various nanomaterials, noble metal Au nanoparticles (NPs) in particular, have received tremendous attention [5-14]. Under AC electromagnetic field (light), free charge carriers in Au NPs are driven into collective oscillations, displaying unique optical phenomena termed as localized surface plasmon resonance (LSPR). This intense light-matter interaction enables huge enhancement of local electromagnetic field, and has been widely...
nanostructures can display unique linear and strong photosensitizers in phototherapy and nonlinear optical behaviors, enabling their use as particle, alloy, heterodimer, core-shell, etc. Au and targeting capability [35, 36]. The development of large surface areas that can be conveniently biocompatible polymers with good biocompatibility different moieties, such as antibodies, peptides, and functionalized with various biomolecules by means of Au-thiolate chemistry, facilitating the attachment of diverse biomedical applications [45-50].

Hybrid nanostructures composed of multiple domains with different compositions have attracted great interests in diverse research fields. For biomedical applications, hybrid nanostructures can provide multimodal imaging modality or imaging-therapy capability all-in-one single unit. More specifically, since Au possess excellent X-ray attenuation ability and high photothermal transduction efficiency, combining Au NPs with metal oxides or metal chalcogenides would either provide complementary imaging modality for accurate cancer diagnosis or offer additional therapeutic avenue for enhanced cancer treatment, thus overcoming the limitation of single theranostic model. Hence, the combined characteristics of Au-based nanostructures would be extremely valuable for their potential applications in precision nanomedicine. Moreover, the construction of plasmonic Au NPs based hybrid nanocomposites may effectively incorporate light absorption, magnetic response, and thermal effect in one single nanostructure. The mutual interaction between Au NPs and neighboring nanomaterials at the nanoscale contact can generate complex interfacial behaviors, such as electron transfer and near-field enhancement, which may induce changes in the effective carrier concentration and optical resonances [51-54]. This plasmon-driven carrier density change and near-field effect in nanohybrids can lead to potential synergistic performance enhancement when compared to the simple sum of the isolated individual components. For example, it is demonstrated that Au NPs can activate the adjacent semiconductors or metal species, enabling increased photoenergy conversion or enhanced light-absorption properties, thus promoting reactive oxygen species (ROS) generation, photoacoustic signal amplification, and heat generation [55-57], benefiting the biomedical outcomes of photodynamic therapy (PDT), photoacoustic (PA) imaging, and photothermal therapy (PTT). Therefore, designing Au-based nanohybrids is a desirable strategy to achieve enhanced theranostic efficiency without increasing the dose of NPs applied, thus averting potential side effect [58-66]. These promising features together with their ease of surface modification make noble metal Au-based nanocomposites a powerful platform for diverse biomedical applications [67-73].

Some excellent reviews have summarized the advances of using noble metal NPs in the field of nanomedicine such as drug delivery, phototherapy, and biosensing [74-76]. However, reviews focusing specifically on Au NPs-based inorganic hybrid nanostructures for biomedical applications are still rare. In this review, we will focus on the design and synthesis of Au-based inorganic hybrid nanostructures, and their improved performance when being applied in the field of nanomedicine, such as bioimaging, cancer therapy, and drug delivery [77-81]. For the choice of adjoining components to Au, we limit our selection to copper chalcogenide, iron oxide, and manganese oxide, which are bioactive nanomaterials that can provide complementary theranostic potential to Au (as schematically illustrated in Figure 1). For each type of nanohybrid, a few important aspects will be discussed including the design and preparation of hybrid nanostructures, interaction between noble metal Au and the adjoining components, as well as their biomedical performance as theranostic agents (as briefed in Table 1).

**Au-Cu₂xE nanocomposites in nanomedicine**

Other than the most researched noble metal nanocrystals, recent studies find that heavily-doped semiconductor nanocrystals such as non-stoichiometric copper chalcogenide NPs (Cu₂xE, where E = S, Se, Te; 0<x≤1) with different compositions can also support LSPR, due to their positively charged free carriers [82-86]. This opens up a new field for plasmonic research [87-94], as LSPR of semiconductor nanocrystals can be easily tuned from...
visible to NIR by simply changing their doping levels. For biomedical applications, the emergence of copper chalcogenide nanocrystals circumvents the limitations experienced when using NIR absorbing anisotropic Au nanocrystals, which are generally large in size and unstable under laser irradiation conditions. Moreover, combining the traditional plasmonic noble metal Au with copper chalcogenide has attracted increasing attention in recent years. Many research groups have devoted efforts into constructing dual plasmonic noble metal-doped semiconductor nanocrystal hybrids, and investigated their coupled surface plasmon resonance properties and applications in the fields of catalysis and nanomedicine [77, 95, 96].

Photothermal therapy

By changing the doping levels either chemically or electrochemically, the LSPR of Cu2-xE can be tuned dynamically, showing characteristic LSPR peaks extendable to the second NIR (NIR-II) window (1000-1350 nm), which is the optimal biological transparent window with larger optical penetration depth and higher maximum permissible exposure of light irradiation over the traditional NIR-I window (700-950 nm) [97-101]. Through the construction of dual plasmonic nanohybrids, the LSPR coupling between Au and Cu2-xE may open up a new regime for designing photo-absorbers with enhanced photothermal efficiency, an attractive attribute for imaging and therapy applications in the NIR-II window.

Table 1. Summary of Au-based inorganic hybrid nanostructures used in nanomedicine

| Hybrid structure | Synthetic method | Size | Application | Advantage | Ref. |
|------------------|------------------|------|-------------|-----------|------|
| Au-Cu2-Se UFO-shape | Seeded growth method | ~22 nm (TEM) | PTT-CT | Improved heating effect | 77 |
| Au-Cu2-Se heterodimer | Seeded growth method | ~10 nm (TEM) | PA | Deep tissue imaging up to 17 mm | 78 |
| Au-Cu2-Se core-shell | Anion exchange | 85.8±10 nm (DLS) | SERS/PA-PTT | Bimodal imaging-guided PTT | 79 |
| Au-CuS@MN@SiO | Seeded growth method | 107 nm (DLS) | PTT-MRI | MRI tacking drug release | 80 |
| Au@CuS@Au hollow structure | Template method | 100 nm (TEM) | PTT-chemotherapy | Photo-switchable targeting | 96 |
| Au-Cu2-S/Se core-shell or heterodimer | Seeded growth method | Tunable (TEM) | N.A | N.A | 102 |
| Au@Cu2-S/Se core-shell | Self-assembly | Tunable (TEM) | PTT-PA-CT | High photothermal conversion efficiency | 103 |
| Cubic CuS@spicky Au core-shell | Template method | 78±5 nm (DLS) | PTT-SERS | Enhanced PTT and SERS | 109 |
| Au-CuS yolk-shell structure | Template method and anion exchange | Tunable (TEM) | PTT-PDT-chemotherapy | Enhanced PTT and PDT | 110 |
| Au-Cu2-S core-shell | Template method | 150 nm (TEM) | Chemo-PTT | Enhanced photothermal effect | 111 |
| FeOx/Au core-shell | Seeded growth method | 6.3 ± 0.7 nm (TEM) | Hyperthermia | Improved hyperthermia | 121 |
| FeOx/Au cluster/shell | Seeded growth method | 240 nm (TEM) | SERS-magnetic hyperthermia | Improved hyperthermia | 122 |
| Fe@Au bi-layer semi-shell | Nanolithography and physical vapor deposition | 40 nm (TEM) | CT, MRI, and fluorescence | Magnetically amplified photothermal therapy | 123 |
| FeOx/Au cluster/shell | Seeded growth method | 126±11 nm (TEM) | PTT-magnetic hyperthermia | Bimodal thermo-therapy | 124 |
| Fe@FeOx heterodimer | Seeded growth method | 11-14 nm (TEM) | MRI-CT | Bimodal imaging | 136 |
| FeOx/Au core-shell | One-pot hydrothermal | 262.7±3.06 nm (DLS) | MRI-CT | Bimodal imaging | 137 |
| FeOx/Au core-shell | Seeded growth method | 22±1.9 nm (TEM) | MRI-CT | Bimodal imaging | 138 |
| FeOx/SiO2@Au core-shell | Seeded growth method | 22±1.5 nm (DLS) | MRI/CT(PA) imaging | Bimodal imaging | 140 |
| FeOx/Au core-shell | Seeded growth method | 179 nm (DLS) | SERS-PA-PTT | Tri-modal imaging-guided PTT | 141 |
| FeOx/Au yolk-shell | Seeded growth method | 65 nm (TEM) | MRI-PA-PET-chemo-thermal therapy | Multimodal imaging-guided chemo-thermal therapy | 142 |
| FeOx@Au@MR@SiO2 core-shell | Seeded growth method | 18.4 ± 2.3 nm (DLS) | PTT-PDT | Enhanced PDT | 143 |
| Au-FeOx heterodimer | Seeded growth method | 16.7 ± 2.3 nm (TEM) | X-ray protection and X-ray enhancing agents | Discriminate healthy cell and cancer cell | 144 |
| MN@Au core-shell | Assembly | 140 nm (TEM) | Nanozyme | Nanozyme-catalyzed cascade reaction | 145 |
| Au@MnO core-shell | Seeded growth method | 50 nm (TEM) | Radiotherapy | Overcoming the hypoxia-associated radiotherapy resistance | 158 |
| CuS@Au (Au@MnO core-shell) | Seeded growth method | 91 nm (TEM) | PDT | Boost immunogenic PDT | 159 |
| Au@MnO core-shell | Seeded growth method | 60 nm (TEM) | PTT | Redox-activated MRI-guided PTT | 162 |
| Au@MnO core-shell | Seeded growth method | 230 nm (TEM) | Dark field imaging | Monitoring cell membrane vesiculation | 163 |
| Au@MnO core-shell | Bio-templated method | 20-25 nm (TEM) | Fluorescent and MRI based sensing | Inherent cross-validation | 164 |

Abbreviations: PTT: photothermal therapy; PDT: photodynamic therapy; PA: photoacoustic imaging; CT: computed tomography; MRI: magnetic resonance imaging; SERS: surface enhanced Raman scattering; MSN: mesoporous silica nanoparticle; TEM: transmission electron microscopy; DLS: dynamic light scattering.
In 2014, our group constructed a dual plasmonic hybrid Au-Cu$_9$S$_5$ with well-controlled interfaces [77]. Using the high purity heterodimer nanohybrid, we investigated the LSPR coupling effect originating from the collective electron and hole oscillations in the hybrid system, and found that the synergistic interactions between two components contributed to their enhanced photothermal performance in the NIR-II window. When comparing the molar extinction coefficient of the hybrid NP to that of its individual components (Au and Cu$_9$S$_5$), the Au-Cu$_9$S$_5$ hybrid showed a 50% enhanced absorption at 1064 nm compared to pure Cu$_9$S$_5$ NPs synthesized using the same protocol (Figure 2A). This enhanced NIR absorption further translated to improved heating capability (Figure 2B), as shown clearly in the thermal images (Figure 2C). The light penetration depth in the NIR-II window was also explored and a decay length of 5.3 mm at 1064 nm was determined. The experimentally measured photothermal performance and theoretical calculations revealed strong LSPR interaction between Au and Cu$_9$S$_5$ domains in the nanohybrids. When being used for in vivo photothermal therapy, more than 10 °C increase was observed at tumor site under 1064 nm laser irradiation at a power density of 0.6 W cm$^{-2}$, which is higher than the required effective temperature for cancer photothermal therapy (42-45 °C), thus inducing significant tumor ablation (Figure 2D). By combining X-ray computed tomography (CT) imaging and photothermal therapy capabilities in one nanostructure, the Au-Cu$_9$S$_5$ nanohybrids were demonstrated to be an attractive multifunctional platform for theranostic application. As the first report on efficient photothermal therapy in the NIR-II windows with power density lower than laser safety standards (1 W cm$^{-2}$, ANSI Z136.1-2007, American National Standard for Safe Use of Lasers), this work reveals that constructing dual plasmonic nanostructures and optimizing the coupling effect of LSPR in nanohybrids is an efficient strategy to design better-performing theranostic agent in the NIR-II window.

Following the work of Au-Cu$_9$S$_5$ nanohybrids construction, various synthetic methods have been deployed to integrate Au in different shapes with copper chalcogenides to form dual plasmonic nanostructures of tunable geometries, in order to explore their LSPR coupling effect and enhanced photothermal capacity. To establish a more general strategy for synthesizing dual plasmonic nanocomposites, our group developed a facile aqueous phase synthesis route to integrate plasmonic Au with self-doped semiconductor Cu$_2$Se [102]. Using a Se-mediated approach, Au-Cu$_{2-x}$Se hybrid nanocrystals with different Au core morphologies such as
nanoparticle, nanorod, and nanotriangle can be facilely synthesized. Moreover, Au-Cu$_{2-x}$Se hybrid nanocrystals with different morphologies such as core-shell and heterodimer geometry can be obtained by varying the polymers used for nanocrystal stabilization. Independently, Xia and coworkers developed a general and eco-friendly method to synthesize core@shell Au@Cu$_{2-x}$E (E = S, Se) dual plasmonic nanohybrids in aqueous solution for multimodal imaging and tumor therapy applications [103]. Due to the plasmonic coupling between noble metal core and semiconductor nanoshell, the as-prepared hybrid Au@Cu$_{2-x}$S showed an extremely large extinction coefficient of 9.32 L g$^{-1}$ cm$^{-1}$ at 808 nm. Another approach for obtaining Au@Cu$_{2-x}$S core@shell NPs with independently tunable core and shell morphology was developed by Zhang et al., through a cation exchange enabled non-epitaxial strategy [95], where the nonstoichiometric composition and thickness of the Cu$_{2-x}$S shell can be precisely controlled.

### Photoacoustic imaging

Photoacoustic (PA) imaging modality is based on measuring the acoustic waves generated in biological tissues after short laser pulses excitation [104-106]. By combining the advantage of high spatial resolution from optical imaging and large penetration depth from ultrasound detection, PA imaging has become a fast-developing imaging technique with great potential in biomedical and clinical applications [41]. PA imaging contrast depends on the optical cross sections of the tissue and the injected imaging agents. Therefore, strongly absorbing plasmonic nanocrystals including Au and copper chalcogenides have been selected as candidates for PA imaging contrast enhancing agents [107-109].

![Figure 2](http://www.thno.org)
Based on the plasmonic coupling induced enhanced photothermal response of Au-copper chalcogenides nanohybrids, Swihart and coworkers have reported using Au-Cu$_{2-x}$Se heterodimer nanocrystals as contrast agents for deep tissue PA imaging [78]. The Au-Cu$_{2-x}$Se heterodimer NPs exhibited a broad optical absorption spectrum across both NIR-I and NIR-II window, as a result of electron transfer between the constituting Au and Cu$_{2-x}$Se domains (Figure 3A). Under 1064 nm excitation, with a power density (10 mJ cm$^{-2}$) at only 1/10 of the ANSI safe limit, sentinel lymph node (SLN) mapping up to 17 mm under skin was achieved (Figure 3B), demonstrating their potential for clinical applications.

As photothermal and photoacoustic effects are intrinsically related to the light-matter interaction, the dual plasmonic Au-copper chalcogenides nano-hybrids are perfect candidates for PA imaging-guided photothermal therapeutic applications operating at the same NIR window. Nie et al. reported aqueous phase synthesis of Au@Cu$_{2-x}$S core-shell NPs via anion exchange between S$^2-$ and Au@Cu$_2$O core-shell NPs, which were then used for accurate tumor identification and efficient ablation through PA imaging-guided photothermal therapy (Figure 3C) [73]. The idea of chemical conversion from Cu$_2$O to CuS using S$^2-$ was further utilized for smart theranostic agent design [81]. A characteristic physiological feature of colon cancer is the high level of endogenous hydrogen sulfide (H$_2$S). Yang and coworkers have shown that the photothermal conversion efficiency of Au@Cu$_2$O increased 50% in the presence of NaHS. Moreover, after intratumoral or intravenous injection, in situ sulfidation of Au@Cu$_2$O by endogenous H$_2$S in colon tumor was confirmed by both photoacoustic imaging (Figure 3D) and Raman spectroscopy. The converted Au@Cu$_9$S$_8$ showed about twice stronger absorption at 808 nm, with increased
photothermic conversion efficiency ~1.2 times higher than the original Au@Cu2O. This work demonstrates that the in situ generated Au-copper chalcogenides nano hybrids, formed by responding to local physiological niche environment at tumor site, can act as smart PA imaging-guided photothermal theranostic agent to treat cancers.

**Activatable drug delivery**

Photothermal therapy can be used to eradicate tumor cells through localized heating. However, unsatisfactory tumor inhibition may occur due to inhomogeneous heating effect at tumor site. Combining chemotherapy with photothermal therapy has shown great promise in cancer treatment, where local heating can be used to regulate drug release with both spatial and dosage control, while the elevated local temperature also improves drug efficacy in treating cancer. To enable higher drug loading capacity, voids are often introduced into the nano-hybrid design. For instance, Lin et al. described the synthesis of hollow CuS@Cu2S@Au nanostructures, which not only exhibited enhanced photothermal conversion efficiency, but also afforded high drug loading capability by providing large cavity and mesoporous shell, thus enabling photo-responsive drug release under NIR laser excitation [96]. Zhang’s group developed Au@void@CuS yolk-shell nanostructures as multifunctional drug carriers [110]. After doxorubicin (DOX) loading, the resultant DOX-Au-CuS yolk-shell nanocomposites could kill cancer cells more efficiently than the unloaded NPs under the same 980 nm laser irradiation conditions, due to the simultaneous photothermal and chemotherapeutic effect.

Drug delivery vehicles are often responding only to single stimulus such as external light irradiation or endogenous pH environment. Designing drug delivery system responding to multiple stimuli will not only minimize the undesirable release of chemotherapeutics thus avoiding adverse side effects, but also maximize the drug dosage in the target region with improved drug availability. To reach this goal, Cao et al. designed a dual responsive drug release system utilizing a rattle-type Au@Cu2S hollow mesoporous structure [111]. With this structure, a high drug loading capacity of 908 μg DOX per mg of the hollow mesoporous nanocrystals was achieved. More importantly, the obtained hybrid nanostructures displayed both endogenous pH- and external photo-responsive drug release behaviors. The acidic pH mimicking tumor microenvironment and NIR laser irradiation could activate the drug delivery system with over 70% of DOX release in 20 min. This makes Au@Cu2S hollow mesoporous structure a promising agent for chemo-photothermal therapy under photoacoustic imaging guidance, due to their superb photothermal conversion efficiency and conspicuous capability of photo activatable drug release property.

Further integrating activatable drug delivery system with real-time drug release monitoring function would enable patient-specific drug administration and benefit personalized medical treatment. Recently, based on the Au-CuS nanostructures, we have developed a smart drug delivery platform with noninvasive activatable magnetic resonance (MR) imaging capacity for controllable drug release tracking [80]. The smart nanocomposites contained two functional components, which were the inner Au-CuS core for heat generation under laser irradiation and outer mesoporous silica (MSN) shell for drug molecules loading and paramagnetic Gd3+ ions anchoring (Figure 4A). The paramagnetic Gd3+ ions-based chelates were used clinically to accelerate the longitudinal relaxation (T1) of excited protons, thus increasing the longitudinal relaxation rate (r1) and generating enhanced T1 MR images. Under exogenous NIR-II irradiation, localized heating of Au-CuS core would melt the gatekeeper phase-change materials loaded in the MSN shell and trigger pulsed drug release with good on/off control (Figure 4B). With the released drug molecules leaving the hybrid nanocomposites, the accessibility of proton to the paramagnetic Gd3+ ions anchored in the mesoporous channels was significantly promoted, which improved r1 of protons, and resulting in a positive correlation between T1 MR imaging signal and the amount of released drugs (Figure 4C), which was further verified at cellular (Figure 4D) and in vivo levels (Figure 4E).

**Au-Fe3O nano composites in nanomedicine**

Iron oxide (Fe3O4 and Fe2O3) with good chemical stability and biocompatibility has gained tremendous attention in diverse biomedical applications including magnetic resonance imaging, sensing, remote-controlled drug delivery, and magnetic hyperthermia [112-119]. By integrating magnetic iron oxide and plasmonic Au into one single unit, the as formed magneto-plasmonic hybrid nanostructures possess great potential in theranostic applications. Their optical and magnetic properties can be tuned independently by changing the respective nanoparticle domain size, shape, composition, and geometry. The unique attributes of magneto-plasmonic hybrid nanostructures have attracted great interests into their design and application for
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Thermal therapy

Thermal therapy is a promising approach to kill cancer cells with the local temperature at tumor site reaching 42-45 °C. Iron oxide and Au NPs are typical thermal agents that can generate heat to destroy tumor cells through noninvasive interaction with either oscillating magnetic field or NIR light [120]. However, both magnetic hyperthermia and photothermia have their inherent drawbacks. While noble metal Au-based photothermia show high heating efficiency with good spatial resolution, the compromised light penetration depth in living tissues set a limit on its potential clinical applications. On the other hand, magnetic NP mediated hyperthermia employs radiofrequency, thus overcoming the penetration depth limitation of photothermia. Unfortunately, magnetic hyperthermia utilizing biocompatible iron oxide NPs suffers from their low specific loss powers. Extensive efforts have been put into modulating the size, magnetization or anisotropy of magnetic particles to enhance their specific absorption rate, thereby improving their heat generation capacity. Designing magneto-plasmonic nanostructures through hybridizing noble metal Au with magnetic nanomaterials together has been explored to overcome the limitations set by the individual components. It was found that by capping...
magnetic NPs with Au, more local heat could be generated when the hybrids were put under a radiofrequency field. Challa S. R. Kumar et al. demonstrated that superparamagnetic iron oxide (Fe3O4) NPs (SPION, 5.4 nm) coated with 0.4-0.5 nm thick gold nanoshell can generate 4-5 times more heat compared to that of the pure Fe3O4 NPs under a low-frequency oscillating magnetic field [121]. They speculated that the higher heat generation capacity was attributed to larger magnetic anisotropy of the superparamagnetic Fe3O4 NPs inside Au shell. Zhou’s group reported a similar study recently [122]. Under the same magnetic induction conditions, a local temperature of 15 °C higher was achieved with the hybrid Fe3O4/Au cluster/shell nanostructures compared to that of the pure Fe3O4 NPs, and induced higher percentage of cancer cell apoptosis. Furthermore, the Fe3O4/Au nanostructures possessed high transverse relaxation rate (r2) for MR imaging (MRI), while the Au nanoshells can be used as surface enhanced Raman scattering (SERS) substrate for early diagnosis. SERS is a surface enhanced optical phenomenon, as Raman signals from surface-absorbed molecules are significantly amplified, due to the strongly enhanced near-field on the surface of noble metal NPs as the result of LSPR excitation. SERS allows optical sensing with high spatial resolution and sensitivity down to single molecule level under optimal conditions. Other than improving magnetic hyperthermia, photothermal effect can also be magnetically amplified via magnetophoretic manipulation strategy, as illustrate in the work by Sepúlveda et al. [123], where the optical heating efficiency of the Fe/Au nanodomes could be dramatically enhanced by local NPs enrichment in the laser irradiation zone under the assistance of an external magnetic field. In addition to single hyperthermia modality, magnetic hyperthermia and photothermia can be synergistically integrated in a properly designed magneto-plasmonic nanohybrid. Abou-Hassan and coworkers synthesized Au nanoshell coated iron oxide multi-core magneto-plasmonic nanohybrids with diameter of around 30 nm [124]. They demonstrated that the heat generated by the magneto-plasmonic nanohybrids display a cumulative effect when both magnetic and plasmonic heating modalities are working simultaneously. With the treatment dose only 1/10 of that used in typical magnetic hyperthermia therapy, a rapid temperature increase to 48 °C could be achieved in tumor tissue under simultaneous magnetic induction and laser irradiation treatment.

**Multimodal MR/(CT, PA, SERS) Imaging**

Biomedical imaging is important for early diagnosis and treatment evaluation, which has emerged as a key technology for the development of targeted therapies. Combining multiple imaging tools together can be very helpful in personal and precision medicine. While molecular imaging tools such as positron emission tomography (PET), computed tomography (CT), and FO (fluorescence optical) imaging have been widely used in clinical diagnostics, each of these imaging methods possesses its own strengths and weaknesses. In recent years, integrating different imaging modalities together by designing multimodal imaging agents such as CT/MR, FO/MR, PA/MR, and SERS/MR have been suggested to obtain more comprehensive pictures for accurate cancer diagnosis [125-132]. By integrating magnetic nanomaterials with Au, the concomitant MR imaging modality can provide non-invasive imaging, large penetration depth, and good soft tissue contrast.

Hybrid Au-Fe3O4 nanocomposites are considered potential bimodal CT/MR imaging agents [133-135], where Fe3O4 component serves as T1 or T2 MR contrast enhancer, while Au with efficient X-ray attenuation capability works as powerful CT contrast enhancing agent. Gu et al. fabricated Au-Fe3O4 heterostructures for bimodal MR/CT imaging application by a seeded-growth method [136]. The prepared Au-Fe3O4 heterostructures were composed of 14 nm Fe3O4 attached to 11 nm spherical Au NPs. The r2 value of the heterostructures was determined to be 136.4 mM⁻¹ s⁻¹ at 1.5 T. Using a rabbit model, the Au-Fe3O4 heterostructure composites exhibited excellent MR/CT contrast enhancing performance. The rabbit liver can be clearly observed by MR imaging. Meanwhile, the detailed anatomical structures such as rabbit right ventricle can be clearly viewed by CT imaging. Using a facile one-pot strategy, Shi et al. reported core-shell Fe3O4@Au nanostructures for bimodal MR/CT imaging application [137]. The MR and CT performance evaluation showed that the hybrid NPs possess high r2 relaxivity (146.07 mM⁻¹ s⁻¹) and excellent X-ray attenuation ability, which was then successfully applied to aorta CT imaging and liver MR imaging in mouse models. In another study, the same group fabricated Fe3O4/Au nanocomposites based on a layer-by-layer (LBL) strategy [135]. Their results demonstrated that at the optimized molar ratio of Au to Fe3O4, Fe3O4/Au NPs exhibited excellent X-ray attenuation characteristics and a relatively high r2 relaxation rate of 92.67 mM⁻¹ s⁻¹. By further modifying them with targeting molecule folic acid, the hybrid nanocomposites could be specifically uptaken by cancer cells that over express folic acid receptors on cell membrane surface. Similarly, Zhang and Wang’s group reported the use of lectin conjugated Fe3O4@Au as bimodal MR/CT imaging
agent in vivo, targeting specifically the colorectal cancer [138].

Besides attenuating X-rays for CT imaging, Au is also excellent PA imaging agent due to their LSPR characteristics. The construction of bimodal MR and PA molecular imaging agents can overcome the limitation of finite penetration depth of PA imaging, and provide structural and functional information of disease with high resolution and sensitivity. Melancon et al. fabricated multifunctional super-paramagnetic Fe₃O₄@Au nanoshells with excellent PA imaging performance and high 𝑟² relaxivity of 208 mM⁻¹ s⁻¹ [139]. Based on the high NIR absorption and strong magnetic properties of Fe₃O₄@Au nanoshells, the hybrid Fe₃O₄@Au nanoshells were capable of lighting up tumor region with PA-MR imaging. Moreover, the bimodal PA and MR imaging can be used to monitor the therapeutic treatment outcome mediated by the photothermal effect of Fe₃O₄@Au. Functionalizing Au-Fe₃O₄ nanocomposites with targeting ligand could further improve their diagnostic capability. Franchini et al. synthesized a multilayered Fe₃O₄@SiO₂@Au core-shell nanostructure conjugated with folic acid [140]. With hydrodynamic diameter of 222±1.5 nm, the as-prepared nanostructure showed bimodal MR/PA imaging ability. After systemic injection into a tumor bearing mice, PA imaging revealed that Fe₃O₄@SiO₂@Au had exclusively accumulated in the ovarian cancer region after 4 h. These studies demonstrate the great potential of utilizing Au-Fe₃O₄ hybrid nanostructures as bimodal MR/CT(PA) imaging agent for in vivo diagnostic applications. It is noteworthy that the biomedical imaging performance of hybrid nanostructures is strongly associated with their specific geometric arrangement. While both Au-Fe₃O₄ heterostructure and Fe₃O₄@Au core-shell nanostructure can be used for bimodal MR/PA imaging, the core-shell Fe₃O₄@Au nanostructures with LSPR located in the NIR region are obviously more suitable for biomedical MR/PA imaging.

Zhang’s group has investigated the potential of using Au-Fe₃O₄ hybrid nanocomposites as multimodal SERS/PA/MR imaging-guided photothermal therapeutics by designing Fe₃O₄@Au core-shell structure (Figure 5A-B) [141]. The combined tri-modal imaging modality (SERS/PA/MR) can provide complementary information of anatomical tumor localization and tumor resection margin for accurate tumor diagnosis and surgical treatment guidance (Figure 5C-E). Furthermore, due to strong NIR absorbance derived from Au nanoshell, Fe₃O₄@Au core-shell nanostructures show high photothermal transduction efficiency for cancer therapy. The 4T1 tumor bearing mice administered with Fe₃O₄@Au core-shell nanostructures have shown significant photothermal tumor ablation under 808 nm laser irradiation. These results illustrated that rationally designed magneto-plasmonic hybrid nanostructures can be used for efficient multimodal imaging-guided photothermal cancer therapy.

**Figure 5.** (A) Schematic illustration of Fe₃O₄@Au core-shell nanoflowers for multimodal imaging-guided tumor therapy. (B) Typical TEM image of Fe₃O₄@Au nanoflower structures. In vivo SERS spectra (C) from normal tissue (a) and tumor region (b), T₂-weighted MR images (D), and PA images (E) of a 4T1 tumor bearing mouse injected with either Fe₃O₄@Au nanoflowers or PBS. Images are reproduced with permission from [141], copyright 2015 John Wiley and Sons.
Activatable drug delivery

Under external stimulus such as NIR light and magnetic field, the multifunctional Au-Fe₃O₄ hybrid nanostructures can not only act as in vivo diagnostic imaging agent, but also serve as powerful delivery vehicles for controlled drug release. In recent years, efforts have been put into developing different Au-Fe₃O₄ hybrid nanostructures with high drug loading capacity, versatile targeting ability, and smart drug release capability. Chen and coworkers reported the synthesis of a yolk-shell plasmonic-magnetic hybrid theranostic platform [142], which was composed of a small Fe₃O₄ core encapsulated inside a hollow cavity formed by a porous Au nanoshell. With a relative small size of around 65 nm, the yolk-shell Fe₃O₄-Au NPs displayed a high r₂ value of 149.4 mM⁻¹ s⁻¹, which is ~2.4 times of that from the core-shell structures, indicating that the interfacial interaction of the two components can greatly affect their magnetic properties. In addition, the hollow cavity can be an ideal storehouse for drug loading. After constructing a gatekeeper on the surface using thermosensitive poly(N-isopropylacrylamide-co-acrylamide), thermal responsive drug release is achieved under NIR irradiation. Initially, only weak DOX fluorescence was observed in the cells as a result of fluorescence quenching by Fe₃O₄-Au. Upon NIR exposure for 5 min, both cytoplasm and nucleus of the cells displayed strong red fluorescence, suggesting DOX was released, which was also confirmed in the in vivo study. In addition to light triggered drug delivery, pH responsive release system has also been widely adopted in different drug carrier designs. Recently, the same group developed a magnetic-plasmonic bilayer vesicle by assembling Fe₃O₄-Au janus structure with a pH-responsive polymer for multimodal imaging-guided cancer therapy [79]. The large hollow cavity formed in the assembled bilayer structures enables a high DOX loading capacity. Due to inter-particle plasmonic and magnetic coupling, the assembled bilayer structures displayed enhanced light absorption and high T₂ relaxivity, and exhibited improved MRI/PA contrast and photothermal activity, compared to the individual components. Moreover, the bilayer vesicles can be disassembled in mildly acidic microenvironment (Figure 6A). Therefore, DOX loaded in the hollow cavity can be released from the Fe₃O₄-Au-DOX bilayer vesicles, in response to the decreased pH level in tumor microenvironment (Figure 6B-C). Other than loading chemotherapy drugs, Au-Fe₃O₄ hybrid...
nanostructures can also carry singlet oxygen (1O2) photosensitizers, and act as a potential agent for photodynamic therapy. For example, Rosa-Pardo et al. designed a core-shell Fe3O4@Au@mSiO2 nanostructure with photosensitizer Rose Bengal (RB) encapsulated inside mesoporous silica [143]. Due to the surface plasmon sensitization effect of Au shell, a 1.5-fold enhanced 1O2 generation by RB was detected. Furthermore, Au-Fe3O4 nanocomposites are also efficient ROS generating agents with their intrinsic enzyme-mimic characteristics [144-146]. By deliberately designing hybrid nanostructures with multi-enzymatic activities to achieve cascade reactions, high chemo-dynamic therapeutic efficiency has been demonstrated using inorganic nanohybrids. For example, Shi and Chen et al. constructed mesoporous silica coated Au-Fe3O4 nanostructures [145]. In tumor microenvironment, the Au domain behaves as glucose oxidase-mimicking nanozyme, catalyzing glucose to H2O2 and gluconic acid. At the same time, the adjacent Fe3O4 domain acts as peroxidase-mimicking nanozyme, reacting with the in situ generated H2O2 and producing highly toxic ROS to kill cancer cells.

**Au-MnO2 nanocomposites in nanomedicine**

Besides iron oxides family, manganese oxides such as MnO, MnO2, and Mn3O4 have also been considered as promising candidates for biomedical applications [147-152]. As Mn is one of the essential trace elements in human body, Mn-based nanoparticles such as MnO2 can be utilized and metabolized by the human body. Mn-based complexes are considered as very promising clinical agents for T1 MR imaging. For instance, Mn-dipiridoxyl diphosphate (DPDP) complex Mangafodipir has already been approved as an efficient T1 MR agent for liver imaging. In addition, MnO2 nanomaterials can respond to tumor microenvironment cues such as hypoxia, acidosis, and vascular endothelial growth factor, which can be utilized to amplify their diagnostic and therapeutic performance. For example, MnO2 nanosheets will rapidly decompose and release Mn2+ under mildly acidic and reducing conditions, thus enhancing the contrast of T1 MR imaging [153, 153]. Moreover, the released Mn2+ could initiate Fenton chemistry to kill cancer cells by catalyzing tumor endogenous H2O2 into toxic reactive oxygen species [149]. Therefore, combining MnO2 nanomaterials with the unique LSPR characteristics of noble metal Au can provide a promising theranostic platform as well as form smart probes for versatile biomedic applications both in vitro and in vivo.

**Enhanced radiotherapy/photodynamic therapy**

Au-MnO2, a new kind of smart therapeutic agent, may serve as a potential theranostic candidate in the field of nanomedicine based on their good biocompatibility and tumor microenvironment responsive behaviors [149, 153-157]. The heavy atom Au can absorb X-rays to generate charged particles, and enhance the effect of radiotherapy (RT). Meanwhile, the MnO2 domain can react with endogenous H2O2 in tumor microenvironment to generate oxygen locally, thus overcoming hypoxia-associated RT resistance. For this purpose, Liu et al. designed Au@MnO2 nanosheets [158], and they observed that Au@MnO2 hybrids indeed have enhanced radiotherapy efficiency as designed. In addition, the nanocomposites containing Au and MnO2 NPs also showed enhanced performance as photodynamic agents [159]. In treating metastatic triple-negative breast cancer, core-shell Au nanocage@MnO2 structures were able to boost immunogenic photodynamic therapy (PDT), thus inhibiting tumor growth and metastases. The enhanced therapeutic efficiency is attributed to the tumor microenvironment responsive oxygen generating MnO2 components, which was decomposed at acidic tumor H2O2-rich conditions and produced sufficient oxygen to boost PDT effect originating from the adjoining Au nanocage.

**Responsive imaging**

Novel tumor microenvironment-responsive imaging agents have emerged as a promising class of theranostic agent for imaging-guided cancer treatment. By designing tumor microenvironment responsive nanoprobes, large off/on imaging contrast can be achieved. For example, Meng et al. prepared Au nanostar@MnO2 nanosheet hybrid structure of less than 50 nm in dimension [160]. With strong light absorption from 300 to 800 nm, the as synthesized hybrid can destroy tumor cells effectively through photothermal effect. Furthermore, the hybrid nanostructures displayed enhanced MR imaging capability in the presence of GSH, due to their redox environment responsive MR imaging capability. This study demonstrates the potential of Au-MnO2 nanocomposites as efficient theranostic nanoprobes for activatable MR imaging-guided photothermal therapy. Other than photothermal therapy, many other therapeutic modalities such as photodynamic therapy and chemotherapy have also been integrated with MnO2 components. Lin’s group designed MnO2-Pt@Au25 nanocomposites, which combined photodynamic therapy, chemotherapy, and activatable MR imaging together in one system [161]. The MnO2 nanosheets acted as carrier for both
photosensitizer Au25 and prodrug Pt(IV) loading. In the reducing tumor microenvironment, high level of GSH would be consumed through redox reaction with MnO2 nanosheets and Pt(IV) prodrugs. As a result, both photodynamic therapeutic efficiency induced by Au25 cluster and Pt(II) chemotherapy efficiency were enhanced. More importantly, the reduced Mn(II) ions released from MnO2 nanosheets can increase the MR relaxivity from 401.9 mg\(^{-1}\) s\(^{-1}\) (r1) and 48.8 mg\(^{-1}\) s\(^{-1}\) (r2) to 471.3 mg\(^{-1}\) s\(^{-1}\) (r1) and 49.6 mg\(^{-1}\) s\(^{-1}\) (r2), thus enhancing their corresponding T1 and T2 MR imaging contrasts. Our group has also reported a feasible strategy to decorate various core materials including Au nanoparticle and Au nanorod with the tumor microenvironment-responsive MnO2 shell, which can be utilized as activatable MRI-PTT theranostic platforms for cancer therapy [162].

Smart biosensing platform

Under a dark-field microscope, a special condenser is used to block central light so that a circular light cone is incident on the object at high angle, only allowing oblique rays to hit the object. This blocks zeroth order light, and objects scatter light more strongly will stand out from the non-scattering dark background. Therefore, Au NPs with strong light-matter interaction due to their LSFR characteristics are perfect objects to be imaged under a dark-field microscope. In this regard, Au-MnO2 nanohybrids are gaining interest as smart biosensors for probing complex cellular events. Xia and coworkers developed UFO-shaped Au-MnO2 plasmonic supraparticles with diameter of around 230 nm, and used these anisotropic structures as dark-field contrast agents to probe the nano-bio interaction at the single cell level (Figure 7A-O) [163]. Due to the

Figure 7. Interactions of the UFO-shaped 2D Au-MnO2 nanostructures with different living cells probed by dark-field images and scattering spectra: (A-E) HepG2 cells, (F-J) 3T3 cells, and (K-O) buthionine sulfoximine (GSH inhibitor) pre-treated HepG2 cells. (D, I, N) Time-dependent \(\lambda_{\text{max}}\) of the scattering spectra changes (E, J, O) after entering the cells. (P) Schematic for two different types of transmembrane processes. (Q) TEM image of UFO-shaped 2D Au-MnO2 nanostructures. Images reproduced with permission from [163], copyright 2019 John Wiley and Sons.
flexibility of thin MnO₂ nanosheets, they can be physically deformed and folded during the endocytosis process. By employing dark-field spectroscopy, they visualized the interactions between 2D Au-MnO₂ nanostructures and living cells, and identified two definitely different transmembrane processes (Figure 7P). During the cell membrane wrapping process, the deformation and folding of the thin MnO₂ nanosheets (Figure 7Q) induced effective refractive index changes around Au NPs, rendering the NPs' LSPR scattering red shift with different magnitudes depending on the endocytosis process. On the other hand, the presence of redox species within cells would disintegrate MnO₂, and induce a LSPR blue-shift, which could be employed to mark the complete cell membrane engulfment process. This LSPR modulation approach provides a convenient but efficient way to monitor the dynamic interactions between nanomaterials and cells. In addition to serve as a cellular probe, smart Au-MnO₂ nanocomposites can also be employed for point-of-care testing. Au@MnO₂ hybrid nanocomposites have been developed to detect ascorbic acid (AA) in human serum [164]. The redox reaction between Au@MnO₂ nanocomposites and AA resulted in the degradation of MnO₂, inducing both MR signal increase and fluorescence recovery due to free Mn²⁺ ions released from Au clusters. This Au-MnO₂ nanocomposite-based magnetic/fluorometric bimodal biosensor allows detection of AA in human serum with cross-validation.

Other Au NPs-based nanocomposites

In addition to the above mentioned hybrid nanostructures, some other Au-based nanocomposites including Au-ZnO, Au-TiO₂, and Au-reduced graphene oxide (rGO) have also been developed and utilized as new type of theranostic platforms for biomedical application [165-169]. Metal oxide NPs such as ZnO and TiO₂ can absorb photons and create electron-hole pairs, generating ROS to inhibit microbial or cancer growth. However, they only absorb in the UV region, and their capability of ROS generation is limited by fast electron-hole recombination. By integrating ZnO or TiO₂ with Au NPs, their optical absorption can be enhanced due to LSPR effect, the spectral window is extended to the visible, and the photo generated charge carrier recombination is greatly suppressed, leading to enhanced photocatalytic and PDT activity. For example, Yin et al. synthesized ZnO/Au hybrid nanostructures using a photo-reduction method [165]. It was found that even Au NPs of sizes less than 3 nm deposited on ZnO NPs can greatly enhance the photo-induced charge carriers in ZnO NPs and thus promoting their ROS generation. Their result demonstrated that constructing hybrid nanostructures with Au is an efficient strategy to improve the photodynamic therapeutic effect of metal oxide. Au-TiO₂ NPs is another Au-based hybrid nanostructure with certain physicochemical properties outperforming their respective building blocks. For example, Yin et al. designed Au-TiO₂ nanostructures and explored their ROS generation capacity under ultrasound stimulation [166]. Their results revealed that the hybrid structures exhibited higher ROS generation efficiency and more significant tumor suppression effect than their counterparts without Au growth, demonstrating the potential of using Au-TiO₂ nanoparticle as sonosensitizer for cancer therapy. Another interesting Au NPs-based-hybrid nanostructure is Au-rGO, as demonstrated by Lim et al., where rGO was coated over Au nanorod [167, 168]. Due to high thermal conductivity of rGO and LSPR characteristic of Au nanorods, the prepared Au-rGO hybrid nanostructures exhibited amplified photothermal effect and PA signal intensity, compared to pure Au or graphene oxide/reduced graphene oxide. Moreover, Au can also be integrated with silica layer to form Au@silica nanostructure [169], thus combining the high drug loading capacity of silica with strong photothermal response of Au nanostructures, leading to better cancer cell killing outcome due to the synergistic effect of photothermia and NIR-induced drug release.

Limitations and challenges

As reviewed briefly, many Au-based nanohybrids with enhanced physicochemical properties and bioactivities have been developed to date, which possess the potential to significantly improve cancer treatment outcomes. However, many challenges need to be resolved before they can be successfully translated to clinical usages.

Synthetic challenges

Many synthetic issues remain to be addressed before we can explore the nanohybrids unique properties for nanomedicine. Although a rich library of noble metal Au-based nanocomposites is now available, their syntheses are generally complex with many reaction variables to tune. One critical question is how to establish a facile and general synthetic method that can build up the nanohybrids with the right functional building blocks of proper size, interface, and geometry [170]. Currently, the typical seeded growth route relies on depositing the second component on the seed NP nucleated in situ or synthesized in advance, which can be severely limited by the interfacial energy or lattice matching...
requirements of the different crystalline domains. Moreover, the growth kinetics can be influenced by complicating synthetic conditions such as reaction temperature, concentration ratio of growth material to seeds NPs, and surface property of the seeds. Non-optimized procedures may lead to low yield of nanohybrids at the end of long tedious procedures. Therefore, developing general synthetic route and establishing standardized protocols to reliably prepare high-quality noble metal-based nanocomposites with controllable morphologies is highly desirable for their extensive biomedical applications.

**Biosafety**

For clinical applications, the critical pharmacological behaviors such as biodistribution and biosafety of inorganic nanomaterials remain an under-explored territory. The physicochemical attributes such as NP size, shape, and surface coating are known to affect their cellular uptake, biodistribution, and nanotoxicity. This calls for systematic investigation on the in vivo behaviors of designed nanocomposites. The choice of chemical composition and surface coating is clearly critical for the nanocomposites biocompatibility. In terms of composition, Au NPs are generally considered to be bioinert, while copper chalcogenides and metal oxides may be etched or biodegraded in the body fluid, releasing metal ions and introducing potential toxicity to cells and organs. On the other hand, nanotoxicity is also strongly influenced by NP surface modifications. Surface coating can induce cytotoxicity effect directly or indirectly by influencing the formation of protein corona, and the subsequent cellular internalization and final fate of the NPs. As many of the NP physicochemical properties are highly interconnected, it is challenging to evaluate the cytotoxic effect originating from a single attribute of the NPs. Moreover, issues on the long-term metabolism of inorganic nanomaterials such as decomposition, degradation, and clearance of the nanocomposites from the body need to be addressed before they can be applied for clinical usage [171-177]. Although many cytotoxicity studies on Au NPs have suggested that they possess good biological safety within several weeks, a great risk of the bioinert NPs is that they may stay in the body and induce chronic toxicity over extended time. Therefore, a balanced stability, slow degradation, and fast clearance should be considered for nanohybrids design with proper choice of chemical composition and surface coating. Finally, the in vitro/in vivo models employed in the biosafety evaluation can also influence the behavior and fate of the hybrid NPs, which may render conflicting results.

To obtain accurate and consistent nanotoxicity evaluation, establishing standardized and reliable protocols to systematically investigate the impact of pharmacological parameters of the NPs is fundamentally important for the biosafety study of the hybrid NPs.

**Conclusions and perspectives**

Nanohybrids composed of noble metal Au and copper chalcogenides or magnetic metal oxides have emerged as a unique class of material due to their interesting plasmon-magnetic properties, and the combined diagnostic and therapeutic functional units in one single entity. In this short review, we have summarized some recent developments in building up Au-based inorganic nanohybrids with controlled composition and structure, and highlighted progresses made in their theranostics applications.

Despite substantial progresses that have been made in the field of Au-based hybrid nanomedicine, this field is still at a rather preliminary stage from the standpoint of practical medical applications, especially in terms of biosafety that we have pointed out in the previous section. To address these important questions, several issues need to be addressed. First of all, more comprehensive studies need to be focused on the nanomaterial-biological system interactions, in order to better understand the critical factors determining the biosafety of nanocomposites, which will then be used for better nanomedicine design. Although plenty nanotoxicity studies have already been carried out on Au [36, 178-181], whether the attachment of a second component would affect its cellular behavior and final fate within organisms is still uncertain. It is believed that many physicochemical parameters of nanomaterials such as size, shape, charge, and surface modification can greatly influence the biocompatibility of nanocomposites. Future toxicity investigations on noble metal Au-based nanocomposites should consider all of these complex factors and explore the underlying molecular mechanisms of various factors on gene expression, signaling pathways, and downstream cell metabolism. In addition, when interpreting the interaction between nanocomposites and organism, it is necessary to note that the organisms may behave well and show normal physiological functions for a short period [182]. However, the organisms may suffer subtle but irreversible changes in their genetics after continuous exposure. Therefore, additional long-term toxicity evaluation is needed in the corresponding animal experiments. Moreover, excellent bioavailability and targeting ability is of great importance for highly efficient biomedical
nanotechnologies. The hybrid nanocomposites must avoid rapid clearance during blood circulation and increase their accumulation dosage at the desirable target site. Recently, the cell membrane-cloaking strategy by mimicking nanoparticles with erythrocyte or host cancer cell membrane envelopes has shown great potency in increasing circulation time by inhibiting macrophage recognition and improving targeting ability via homotypic binding [183-187]. However, this technique still faces some inherent challenges. For example, the detailed biomolecular mechanism of the homotypic binding derived from cell membrane is yet unclear. Identification of the specific ligands involved in the host membrane recognition would benefit future development of nanomaterial-based biomimetic nanotechnology. Furthermore, it is very difficult for the nanohybrids to go deep into solid tumors, which severely limits their efficacy as drug carrier and imaging platform. Knowledge on the NPs’ pathway into tumors would be useful in helping design nanohybrids structures with improved tumor penetration depth. Despite the discovery of endothelial gaps in tumor vasculatures using developed animal models, nanomedicine design utilizing the enhanced permeability and retention (EPR) effect for human tumor treatment has been controversial. Only a few anticancer nanomedicines have received approval for clinical application based on EPR effect. Recently, new evidence has emerged, suggesting NPs may enter tumors via an active process through endothelial transcytosis [188]. These observations may establish new paradigms and enable novel strategies to help expedite the clinical translation of nanomedicine.

Au-based multifunctional nanocomposites have shown their promises in both early diagnostic and theranostic applications. Of note, their manifested multifunctionality due to the synergistic effect between different components would enable safer and more effective theranostic treatment. Undoubtedly, with continuing endeavor in the design and development of new multifunctional nanohybrids, it is our firm belief that they hold great diagnostic and therapeutic potential in broad biomedical applications, and are likely to find real significance in the new era of personalized precision nanomedicine.

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Competing Interests

The authors have declared that no competing interest exists.

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