Multifunctional magnetic gold nanomaterials for cancer

Pradip Das,[1] Parisa Fatehbasharzad,[1,2] Miriam Colombo,[1] Luisa Fiandra,[3,*] Davide Prosperi[1,4,*]

[1]NanoBioLab, Dipartimento di Biotecnologie e Bioscienze, Università di Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy. [2]Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università di Torino, Via Nizza 52, 10126 Torino, Italy. [3]Dipartimento di Scienze dell'Ambiente e della Terra, Università di Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy. [4]Nanomedicine laboratory, ICS Maugeri S.p.A. SB, via S. Maugeri 10, 27100 Pavia, Italy.

*Correspondence: luisa.fiandra@unimib.it, davide.prosperi@unimib.it

Keywords

Gold nanomaterials, physicochemical properties, gold-magnetic hybrid, multi-imaging, multi-therapy, cancer theranostics

Abstract

The integration of multiple imaging and therapeutic agents into a customizable nanoplatform to allow for accurate identification and rapid prevention of cancer is attracting great attention. Among the available theranostic nanosystems, magnetic gold nanoparticles are particularly promising as they exhibit unique physicochemical properties that can support multiple functions, including: 1) cancer diagnosis by magnetic resonance imaging, X-ray computed tomography, Raman and photoacoustic imaging, 2) drug delivery and 3) plasmonic photothermal and photodynamic therapies. This review gives an overview of recent advances in the fabrication of multifunctional gold nanohybrids with magnetic and optical properties and their successful demonstration in multimodal imaging and therapy of cancer. Concerns around toxicity of these nanomaterials are also discussed in view of an imminent transition to the clinical practice.

Gold nanoparticles allow developing a new generation of all-in-one therapeutic and diagnostic materials for biomedicine

In recent years, the use of a **multimodal approach** (see Glossary) for cancer management has increasingly acquired importance. The preferred strategy refocused from monotherapy to multitherapy to enhance treatment efficiency, so as to a combination of cancer therapy and diagnosis. In this transformation, nanotechnology is recognized as a key player that is expected to drive such profound transformation. Within this vision, two or more therapeutic agents can be associated into a single **multifunctional nanomaterial** to obtain the benefits of a bimodal or trimodal synergistic therapy. Moreover, the co-assembly of drugs and contrast agents is allowed to originate **theranostic** probes able to exert the detection and cure of tumors at the same time [1].

Over the last decade, gold-based magnetic nanoparticles have attracted interest in the management of **cancer disease** by taking advantage of combined multiple diagnostic and/or therapeutic potentialities. The multifunctional character of gold nanoparticles (AuNPs) is mainly attributable to the unique chemical-physical properties of these nanomaterials, which allows for customization of several diagnostic and therapeutic functions. The potential of AuNPs as a contrast agent for cancer diagnosis has been described for magnetic resonance imaging (MRI) associated with spin-active contrast agents [2,3], X-ray computed tomography (CT) [4], surface-enhanced Raman spectroscopy (SERS) imaging [5] and **photoacoustic imaging** (PAI) [6].

AuNPs also represent an efficient system for plasmonic photothermal and photodynamic therapies (PPT and PDT) [7], **radiotherapy** (RT) [8], and for the delivery of drugs [9] and genes [10]. The potential of these nanocomplexes as theranostic systems with the opportunity of multitherapy for cancer control has been more recently investigated. The present review is aimed to highlight the potential of these Au-based nanotheranostic agents to face cancer through multiple approaches.

Despite the great potential of magnetic AuNPs for **clinical translation**, very limited perspective on this topic has been outlined so far [11-13]. The present report aims to provide an updated and critical insight into the recent literature focusing on hybrid magnetic AuNPs preparation, classification, chemical-physical characterization, and on the advanced methodologies for combined cancer diagnosis and therapy. Concerns around toxicity of these nanomaterials are also discussed in view of a tangible transition into the clinical practice.

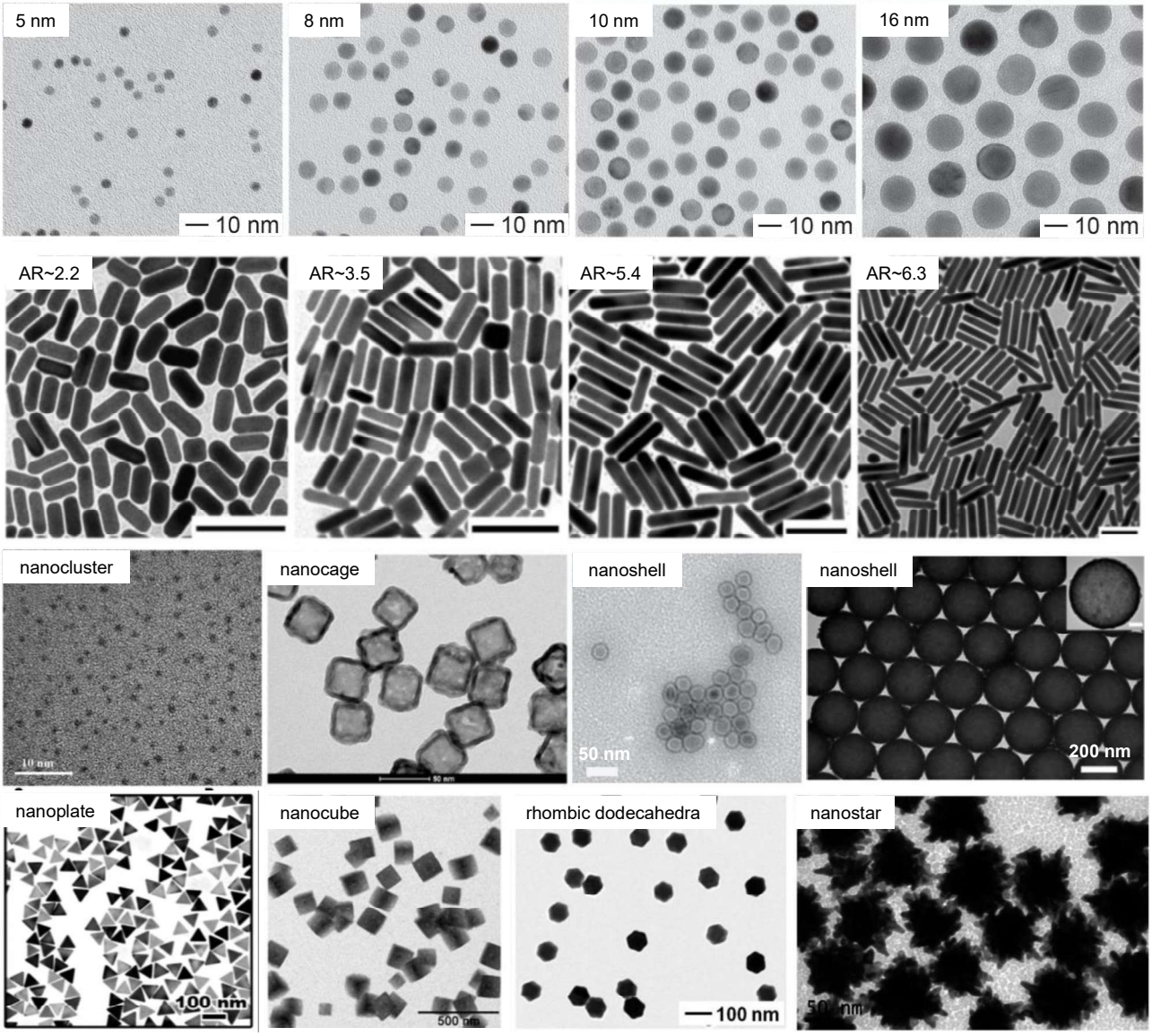


Figure 1. Transmission electron microscopy (TEM) images of various gold nanostructures. The first row shows single-crystal gold nanospheres with different sizes in the range of 5-16 nm. Reproduced with permission from ref. [18] Copyright 2014 Wiley-VCH. The second row represents TEM images of gold nanorods with tunable aspect ratio from 2.2 to 6.3. The scale bars of all images are 100 nm. Reproduced with permission from ref. [21] Copyright 2015 Ivyspring. The images of gold nanoclusters, nanocages, and nanoshells are presented in the third row. Reproduced with permission from ref. [16,23,24,26] Copyright 2014 Royal Society of Chemistry, Copyright 2016 American Chemical Society, Copyright 2010 Nature Publishing Group, and Copyright 2016 Wiley-VCH. The other shapes of gold such as nanoplates, nanostars, nanocubes, and rhombic dodecahedra are shown in the last row. Reproduced with permission from ref. [28-31] Copyright 2010 and 2014 American Chemical Society, and Copyright 2010 and 2013 Royal Society of Chemistry.

Gold nanomaterials preparation, classification, chemical-physical characterization

The utilization of biocompatible gold **nanostructures**, including nanocluster, nanosphere, nanorod and nanocage, in biomedicine is more favorable compared to other inorganic nanomaterials owing to their facile synthesis in aqueous solution, straightforward surface modification and unique physiochemical properties [14-31]. The size and shape dependent optical properties of gold nanomaterials, including fluorescence, **localized surface plasmon resonance** (LSPR) and effective absorption of X-rays have been exploited to design multifunctional nanoprobes for cancer diagnosis and treatment. Several approaches have been reported for the synthesis of these gold nanostructures (Figure 1), however, we highlight here the most frequently employed wet methods (Table 1).

The bright fluorescence in the visible to near-infrared (NIR) spectral region of gold nanoclusters (AuNCs) is mainly capitalized on bioimaging applications. Nanoclusters are composed of several to hundreds of gold atoms and can be prepared either by bottom-up or top-down approaches [15,16]. In bottom-up methods, stable nanoclusters are obtained via reduction of gold salts in presence of thiol materials as strong capping agents or peptides as structure-defined scaffolds. The most commonly used reducing agent is sodium borohydride and sometimes the light is also used to avoid hazardous chemicals. Conversely, the etching of AuNPs by thiol ligands produce gold nanocluster in a top-down approach. The optical properties of synthesized gold nanoclusters depend on their physiochemical characteristics such as size, shape and surface chemistry [15].

Gold nanospheres are probably the most widely explored colloidal nanoparticles in biomedicine and most of the reported methods for their synthesis are based on two original methods that were developed by Turkevich and Frens [17]. The reduction of $HAuCl_4$ using sodium citrate in an aqueous solution produces AuNPs of different sizes depending on the ratio of reducing agent to gold salt. Adding a seed-mediated growth step is advantageous to obtain larger nanoparticles [18]. AuNPs are also prepared in a biphasic solution assisted by a phase transfer agent and a capping surfactant [19]. The typical single LSPR peak of small round nanoparticles becomes wider and shifts from 520 nm to higher wavelengths upon increasing size [17].

Among various methods for the synthesis of gold nanorods (AuNRs) with controlled aspect ratio, a simple, highly efficient and reproducible seed-mediated growth method has been extensively exploited over the past decades [20,21]. This method involves the synthesis of small AuNPs by reduction of gold precursors (e.g., $HAuCl_4$) to be used as

seeds for subsequent growth of these seeds into nanorods in presence of growth solution. The anisotropic character of AuNRs results in two characteristic LSPR peaks, one associated to a transverse mode around 520 nm, which is fixed, while the second relative to a longitudinal mode at 600-1800 nm, which is instead dependent on the aspect ratio of AuNRs [20,21]. AuNRs exhibit higher photothermal conversion efficiency compared to spherical nanoparticles and are therefore more appropriate for **photothermal therapy**.

Gold nanoshells can be generated using several colloidal nanomaterials, including silica nanoparticles, iron oxide nanoparticles and quantum dots, which act as a template, by means of deposition of gold through chemical reduction of gold salts [22-24]. The gold layer on these core-shell nanoparticles has thickness-dependent enhanced tunable LSPR properties from visible to NIR region. In addition to their unique optical properties, the combination with the inherent properties of core materials offers the opportunity to develop an efficient multifunctional theranostics platform for cancer.

The hollow interior and porous wall of gold nanocages are fabricated by deposition of reduced gold on the surface of a silver nanocube template followed by spontaneous oxidation of silver through galvanic replacement, producing a colloidal solution with LSPR peak in the range between 400-1200 nm [25]. These amazing nanostructures allow to incorporate therapeutic agents inside their cavity, making them candidates for cancer theranostics [14,25,26].

The progress in the synthesis and characterization of other gold nanostructures including nanoplates, nanostars, and nanocubes has been also well established in the last decades. Most popular methods used for the preparation of these nanostructures are chemical reduction and seed-mediated growth [27-31]. Their optical properties including NIR LSPR peak make them attractive for biomedical applications. Consequently, synthesized gold nanostructures support the development of many different **magnetic gold** nanostructures more (Box 1) [32-42].

Table 1. Summary of various gold nanostructures for the design and synthesis of multifunctional magnetic gold nanocomposite-based cancer theranostics.

nanostructure	synthesis method	characterization	ref.
nanocluster	chemical reduction, photoreduction, chemical etching	bright fluorescence, high two-photon absorption cross-section, good biocompatibility	[15,16]
nanosphere	chemical reduction, seed-	single LSPR peak in the range	[14,17-

	mediated growth	of 520-650 nm, the smallest specific surface area, highest colloidal stability	19, 27]
nanorod	seed-mediated growth, electrochemical reduction, photochemical reduction	two typical LSPR peaks with the tunable longitudinal mode, higher extinction coefficient, enhanced photothermal conversion efficiency, superior scattering contrast agent	[14, 20,21,27]
nanoshell	template-directed synthesis	tunable LSPR features with stronger NIR absorbance and scattering, highly effective for photothermal therapy and surface-enhanced Raman scattering	[14, 22-24]
nanocage	galvanic replacement reaction	large absorption cross-section, tunable LSPR properties from 400 to 1200 nm, hollow interiors and porous walls	[14, 25,26]
others (e.g., nanoplate, nanostar, nanocube, etc.)	chemical reduction, seed-mediated growth, polyol approach, one-pot synthesis	strong LSPR throughout the visible region and NIR region, more effectiveness of branched nanostructure for surface-enhanced Raman scattering	[14,27-31]

1

2

Box 1. Strategies for the Synthesis of Magnetic Gold Nanostructures

Numerous facile synthesis methods have been well established for the preparation of monodisperse magnetic nanoparticles with tunable sizes and shapes over the past decades [32]. Therefore, for making various types of magnetic gold nanostructures, for example, Janus, core-satellite, and core-shell nanoparticles (Figure I) from individual nanoparticles, we describe briefly most commonly used strategies.

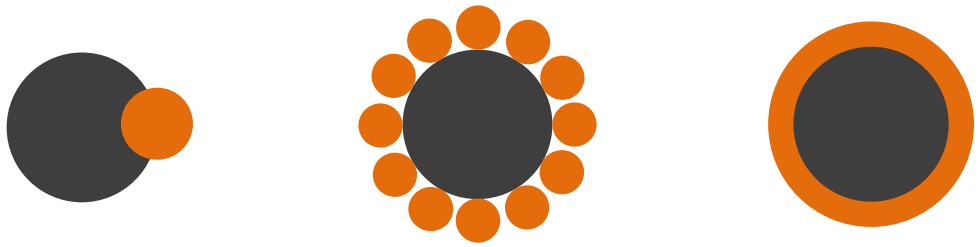


Figure I. Schematic illustrations of frequently synthesized magnetic gold nanostructures for biomedical applications. Black color structures represent magnetic nanoparticles and orange color structures represent AuNPs.

Synthesis of dumbbell-shaped Janus magnetic gold nanostructures involve deposition of single magnetic nanoparticles on each pre-synthesized AuNPs via thermal decomposition of precursors, such as $Fe(CO)_5$ for magnetic nanoparticles, or one-pot method where mixture of precursors, for example, $HAuCl_4$ and $Fe(CO)_5$ for both nanoparticles, are heated simultaneously [33-35]. Synthesized Janus nanoparticles using gold seed are usually monodisperse.

Core-satellite magnetic gold nanostructures consisting of a magnetic nanoparticle core decorated with several smaller AuNPs on peripheral of the core have been prepared by linking separate nanoparticles. These hybrids sometimes act as intermediate for the synthesis of core-shell nanoparticles. In general, negatively charged satellite AuNPs are immobilized on a positively charged inner magnetic nanoparticles via electrostatic interaction [36,37]. Besides, in situ formations of AuNP seeds on the surface of magnetic nanoparticles via reduction of $HAuCl_4$ promote the generation of the core-satellite structure [38,39].

Gold coated magnetic nanoparticles have been prepared by two methods. In the direct method, gold precursor is directly deposited onto the chemically modified surface of magnetic nanoparticles having similar crystal lattices, followed by reduction of gold by reducing agents [23,40]. In contrast, indirect methods necessitate adsorbing first small AuNPs on the magnetic nanoparticles surface as seeds that act as nucleation sites to facilitate the growth of the gold shell upon addition of growth solution [41,42]. The latter method is more favorable for the synthesis of highly monodisperse gold nanoshells with tunable thickness.

Biomedical applications of hybrid AuNPs

A number of imaging techniques including MRI, CT, and PAI as well as therapeutic approaches including PTT, PDT, RT, chemotherapy, and hyperthermia therapy using magnetic gold **nanocomposites** have been developed towards the diagnosis and treatment of several diseases and especially cancer (Figure 2).

Imaging

In view of an accurate detection of occult metastases and due to the need of tissue reconstruction after treatment of highly aggressive cancer, the development of newly designed complex biomaterials, imaging techniques, and specialized imaging probes to sensitively access detailed images of the 3D spatial distribution of malignancies seem vital. The imaging of tissues helps to differentiate the diseases states like tumors from healthy environments. Besides, the progress of cancer therapy can be monitored by bioimaging.

MRI is a **non-invasive technique**, widely employed in molecular imaging and medical diagnosis in the clinic [43]. Contrast agents (CAs), including paramagnetic Gd(III) complexes for T_1-weighted images and superparamagnetic iron oxide nanoparticles for T_2-weighted images, are frequently employed in MRI to enhance imaging sensitivity and accuracy in diagnosis [44]. The magnetic relaxivities of CAs are conveniently improved by combination with plasmonic AuNPs in nanocomposites as a result of surface plasmon-driven enhanced magneto-optical interaction [45]. The fruitful validation of magnetic-gold nanocomposites as efficient CAs, for example, Gd(III)-DNA@gold nanostars and Gd(III)-labeled AuNPs, were demonstrated in MRI of pancreatic cancer with high contrast-to-noise ratios [46,47].

Another widely employed non-invasive imaging and diagnostic clinical technique is CT, which relies on the absorption of X-rays by tissues and is commonly recommended after or in concomitance with MRI [43]. Among recently developed nano-CAs, AuNPs are particularly indicated for CT owing to their intrinsic high X-ray absorption coefficient [48]. Indeed, various magnetic gold hybrids were extensively developed and used as CAs for pre-clinical identification of tumors by CT [49,50].

PAI comes forth as a quantitative and non-invasive real-time diagnostic method used in clinical setups. It benefits from converting the absorbed light into an outgoing

thermoacoustic wave, thus offering a complementary approach to the established imaging techniques [51]. AuNPs have been suggested as CAs for PAI owing to their extremely high absorption of light in the NIR window [52]. For this reason, AuNR-bound magnetic nanoparticles was used in magnetically targeted PAI imaging of cancer [53].

Thanks to high sensitivity and accessible cost, optical molecular imaging is an emerging technique useful for examining the occurrence and progression of the tumor [43]. For example, fluorescence optical imaging (FOI) and newly developed fluorescent biomarkers have been customized for real-time monitoring of physicochemical processes and critical cellular activities associated with tumor insurgence and progression and for multiplexed imaging of cancer foci detection and therapeutic outcome [43,54]. Therein, biosynthesized complexes of AuNCs and iron with high fluorescence properties in the NIR region was more beneficial for early diagnosis of malignant tumors basing on fluorescence imaging [54]. Two-photon luminescence (TPL) flourished as one of the most powerful bioimaging tools for imaging and tracking at the microscopic level with high resolution [55]. Due to plasmon modes of metallic nanostructures AuNPs can be used as TPL emission resources for imaging of **tumor microenvironment** [56]. Plasmonic nanostructures significantly enhance the signal emission compared to single fluorescent dye molecule [57]. Furthermore, magnetic AuNPs can improve surface plasmon oscillation and non-radiative decay of excited AuNPs by an effective magneto-optical coupling, which is suitable for multimodal imaging [45]. The nanocomposite of AuNPs with IONPs provided bright TPL images of cancer cells [58].

SERS imaging is another promising and complementary optical modality for surface-sensitive biomedical imaging that allows visualization of molecules distribution in cells with high resolution [59]. The SERS effect of AuNPs is more useful to enhance the sensitivity and specificity to determine intracellular cancer biomarkers accurately with very low noise to signal ratio and multiplexing capability [48]. Thus, AuNPs are an attractive CA for Raman imaging of cancer cells/tumors. Amendola and colleagues designed magneto-plasmonic nanoparticles (Au-Fe alloy) that allowed the identification of tumor by SERS imaging [60].

Therapy

Thanks to their easy surface functionalization and capability of thermal ablation of tumors, AuNPs are gaining popularity in view of an imminent clinical transition. According

to their LSPR, AuNPs convert the absorbed laser beam into heat and kill the tumor cells consequently [61]. However, the application of NIR-assisted therapeutic methods remains challenging in treating deep tumors due to low tissue penetration of light [48]. Eyvazzadeh and colleagues demonstrated the potential of Au-coated IONPs with high NIR light absorption as a candidate for cancer photothermal therapy [62].

Radiotherapy is a crucial therapeutic mode applied for the treatment of nearby 50% of cancer patients [8]. Recently, much interest was raised toward application of AuNPs as **radiosensitizer** in radiotherapy of cancer with special attention to hypoxic solid tumors taking advantage of Au nanostructures high absorption and efficiency in generating secondary electrons under γ-ray or X-ray irradiation [63]. In fact, it has been shown that AuNPs with different sizes and shapes can improve significantly the effectiveness of radiation doses both *in vitro* and in vivo. Yang and colleagues demonstrated that the efficiency of radiotherapy depends on the size-dependent accumulation of magnetic AuNPs at the tumor site [64].

PDT recapitulates important benefits such as negligible invasiveness, capability of being specifically targeted, the possibility of administering repeated doses in contrast to radiotherapy, and minimal or absent scarring after healing [65]. Another advantage of PDT, which is beneficial for the patient, is the possibility of being performed in an outpatient or day-case setting without side effects [65]. Han and colleagues used Gd_2O_3-AuNC hybrids to sensitize the generation of singlet oxygen ($^1O_2$) under NIR laser stimulation in PDT of cancer. The AuNC component in the Gd_2O_3-AuNCs hybrid enhanced the efficiency of PDT increasing the production of $^1O_2$ [66].

Hyperthermia has long been used to treat cancer. Hyperthermia kills or weakens the tumor cells by exposing the body tissues to high temperatures. Since tumor cells are more sensitive to heat compared to non-diseased cells, they could be more susceptible to chemotherapy or radiation therapy after hyperthermia treatment [48]. Notably, magnetic hyperthermia therapy has important clinical advantages because of its ability to destroy deep tumor tissues in a non-invasive manner taking advantage of wide spatial penetration of radiofrequency radiation produced by an alternating magnetic field [32]. Superparamagnetic AuNPs clusters showed typical superparamagnetic behavior and extraordinary magnetic hyperthermia effect, which is more favorable for cancer theranostics compared to simple photothermal therapy [67].

In the past half century, chemotherapy has been one of the most popular cancer treatment methods [68]. In conventional chemotherapy, delivery of anticancer drug to tumor cells is performed by the circulatory system. Therefore, this method needs high concentrations of drug administered to the patient to reach tumor cells and since it is not tumor-targeted, system toxicity and side effects of the drug are generally high [68]. Therefore, being able to deliver the drug to specific tumor tissues, nanoformulations become an attractive alternative to traditional chemotherapy. Magnetic assisted drug delivery systems outperform other targeting techniques exploiting a variety of energy sources such as electromagnetic fields and ultrasounds [69]. In magnetic targeted drug delivery (MTD), magnetic nanoparticle surface is modified with an appropriate biocompatible coating to allow drug loading. Therefore, highly accumulated drug molecules at the tumor site using an external magnetic field exhibit enhanced anticancer activity with limited side effects. The characteristics of AuNPs such as plenty of preparation methodologies and ease of surface functionalization make them potential candidates for modifying MNPs with versatile profunctional nanostations [48]. For example, Peng and colleagues reported mesoporous magnetic gold for targeted delivery of drug to the breast tumor site by exposure to an external magnetic field [70].

Box 2. Advantages and Disadvantages of Various Imaging and Therapy Modalities

magnetic resonance imaging

advantages: non-invasiveness, high spatial resolution, unlimited tissue penetration depth, no involvement of radiation

disadvantages: relatively low sensitivity, long processing time

remarks: enhanced relaxivity of magnetic AuNPs based CAs increased the sensitivity

computed tomography

advantages: non-invasiveness, high spatial resolution, unlimited tissue penetration depth

disadvantages: involvement of high dose ionizing radiation, low sensitivity

remarks: AuNPs based superior CAs reduced the false positive results

photoacoustic imaging

advantages: fast imaging, high spatial resolution, highly sensitive, 3D image reconstruction

disadvantages: low tissue penetration depth, photo-toxicity to surrounding tissues

remarks: high effectiveness of AuNPs with magnetic properties as CAs in photoacoustic imaging of tumors

fluorescence imaging

advantages: non-invasiveness, highly sensitive, multiplex imaging

disadvantages: poor tissue penetration depth, high photobleaching, photo-toxicity to tissues, low spatial resolution

remarks: highly photo-stable fluorescence properties of magnetic AuNPs was more successful for imaging of tumor cells/tissues

surface enhanced Raman spectroscopy (SERS) imaging

advantages: high sensitivity, multiplex imaging, first signal acquisition

disadvantages: laser-induced photodamage of tissues, interference by fluorescence

remarks: optical properties of AuNPs improved signal to noise ratio

photothermal therapy

advantages: low cost, minimal invasiveness, high specificity

disadvantages: photodamage of healthy tissues by high power laser, restricted tissue penetration aptitude of laser

remarks: magnetic AuNPs with higher photothermal conversion efficiency successfully inhibited tumor growth using low power laser

photodynamic therapy

advantages: slightly invasive, low cost compared to others, localized treatment, rapid and repeatable

disadvantages: less effective for large and hypoxic tumor, side effects by laser irradiation

remarks: multifunctional magnetic AuNPs enabled to supply oxygen into hypoxic tumor

magnetic hyperthermia

advantages: high susceptibility of tumor cells to heat, tumor homing of heat mediators by

external magnetic field, higher tissue penetrating power of magnetic field

disadvantages: non-homogeneous distribution of heat mediators into tumor, lack of more efficient heat mediators

remarks: combination with other therapies using magnetic AuNPs improved the efficiency

radiotherapy

advantages: more effective for rapid cancer treatment, lower recurrence rate, superior cure rate

disadvantages: use of high dose ionizing radiation, damage of surrounding healthy tissues, limited to treat hypoxic solid tumors

remarks: magnetic AuNPs worked as radiosensitizers to reduce the side effects and also overcome hypoxia-induced resistance of ionizing radiation

chemotherapy

advantages: very effective against rapidly growing tumor, reduced the chance of recurrence after surgery, lower acute toxicity compared to radiotherapy

disadvantages: affect healthy cells/tissues, long-term side effects

remarks: multifunctional magnetic AuNPs provided the selectivity to destroy tumor cells only

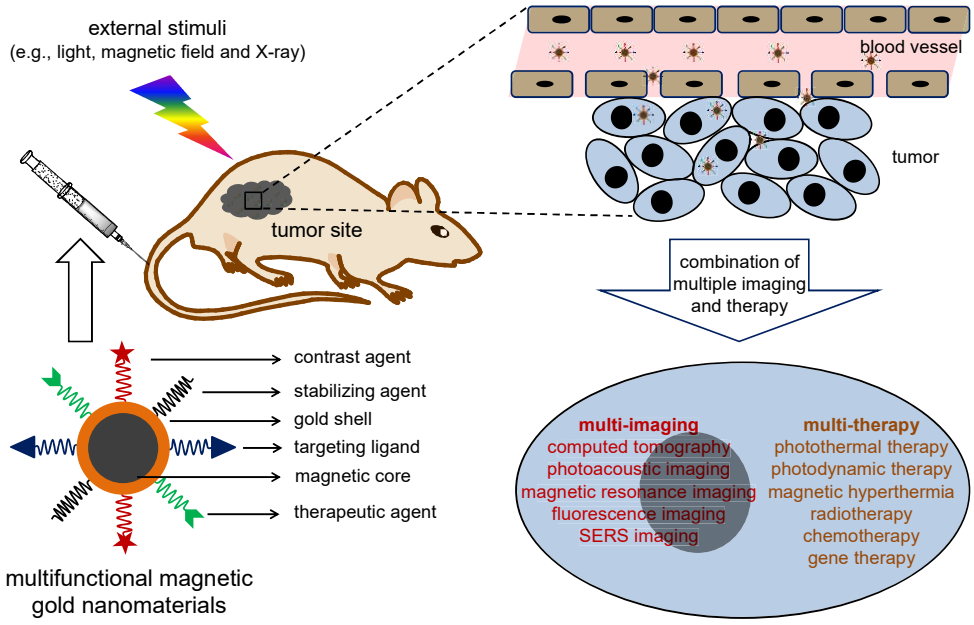


Figure 2. Schematic representation of multifunctional magnetic gold nanomaterials used in multimodal imaging and therapy of cancer with the aim of developing an effective novel cancer theranostics.

Combined AuNPs-based approaches for multi-imaging

The multimodal imaging consists of a combination of more than one non-invasive imaging techniques into a single platform to achieve enhanced spatial resolution and improved sensitivity compared to each individual imaging technique (Box 2). In principle, multimodal imaging is expected to allow the diagnosis of diseases at the early stage and monitoring the therapeutic effects with high accuracy [71]. Biocompatible multifunctional gold nanomaterials endowed with active magnetic properties have successfully established their significant character as an effective CA in order to perform multimodal imaging including CT, MRI, and FOI. For example, Wu and colleagues used Gd^{3+} ion-induced aggregated gold nanoclusters inside silica with enhanced emission for *in vitro* and *in vivo* diagnosis of breast cancer by FOI, MRI, and CT imaging techniques at once [72]. In another study, gadolinium oxide-gold nanocluster hybrids stabilized by BSA protein had greater contrast capability in trimodal imaging (e.g., CT, MRI, and FOI) of cervical cancer cells and *in vivo* system [66]. Kuang research group prepared a biocompatible spiky Fe_3O_4@Au supraparticle with enhanced NIR absorption, which efficiently served as an imaging agent for MRI, CT, and PA imaging of cervical cancer simultaneously [73]. Therefore, such types of multifunctional magnetic AuNPs are more promising agents for the development of cancer theranostics via employment of their therapeutic aptitudes such as photothermal therapy, radiotherapy, and magnetic hyperthermia.

Combined AuNPs-based approaches for multi-therapy

In the last years, the association of multiple therapies in a single nanotool has received remarkable attention to overcome the limitations of monotherapy for cancer treatment (Box 2). The use of AuNPs for multitherapy has been mainly directed to strengthen the efficacy of photothermal therapy by synergistic effects of different therapies.

Magnetic gold nanoshells for multi-therapy

The magnetic nanocomposites with gold nanoshells that exhibit surface plasmon absorbance in the NIR region are more promising for the development of an efficient cancer therapeutic agent via a combination of photothermal therapy with other treatment modalities. In recent years, several such types of multifunctional nanomaterials offering the platform of multimodal image-guided cancer therapy have been reported (Table 2). For example, Yeh research group reported multifunctional nanoparticles based on

mesoporous silica coated Fe_3O_4@Au nanoparticles loaded with anticancer drug doxorubicin followed by oligonucleotide capping for effective treatment of cervical cancer [74]. The enhancement of nanoparticle internalization and production of heat due to the photothermal effect of gold inside the tumor was achieved by application of an external magnetic field followed by NIR laser excitation, which facilitated the drug release in a controlled manner. Therefore, collective anticancer activities exposed significant therapeutic effects towards tumor tissue that allowed removing the tumor completely after 14 days. Similarly, Ma and colleagues observed the higher therapeutic effectiveness of CDF-Au shell nanomicelle in cervical cancer treatment owing to the effects of photothermal therapy and magnetic field guided drug delivery simultaneously [75]. Huang research group investigated the effect of multimodal therapy in presence of an external magnetic field in breast cancer treatment using magnetic gold nanopopcorns containing NIR absorbing photosensitizer [76]. The *in vitro* studies exhibited that gradient magnetic field accelerated intracellular uptake as well as the release of photosensitizer agent and as a result, the synergistic effect of photothermal and photodynamic therapies improved anticancer activity compared to that without magnetic field. Recently, the combination of photothermal therapy with radiotherapy using gold-coated IONPs specifically induced the higher level of apoptosis in KB cancer cells that is suitable for treatment of head and neck cancer [77].

Magnetic gold nanomaterial for multi-therapy

The integration of magnetic nanoparticles with gold nanomaterials, particularly AuNRs, into single nanoplatform is estimated to have greater impact in cancer treatment (Table 2). In this section, we provide the effectiveness of these nanocomposites in the management of combination therapy for cancer. The drug-loaded nanocapsule (GNR@IOs-DOX) with superior magneto-plasmonic characteristic and stimuli-responsive drug delivery behavior presented a well-organized multifunctional system for effective cancer treatment [78]. The complete abolition of breast tumor at the early stage without possible recurrence was attained through the combination of magnetically guided tumor homing of this nanocapsule and, subsequently, dual effect of NIR laser triggered increased temperature and released doxorubicin. Hu and colleagues designed and prepared a successful multifunctional polycationic nanocomposite based on negatively charged polydopamine coated IONPs and positively charged AuNRs to complex plasmid DNA for dual therapy of glioma cancer [79]. The combined application of photothermal and gene

therapy had more potentiality in inhibition of high proliferation of glioma. A novel nanocomposite was developed by Yang and colleagues via decoration of plasmonic photothermal agent AuNPs and targeted agent Fe_3O_4 nanoparticles on black phosphorus nanosheet, which performed as photosensitizer [80]. A low-power NIR laser was sufficient to produce combo of photothermal and photodynamic therapies to cervical cancer cells that effectively inhibited the tumor growth. The multifunctional core-shell magnetic AuNPs (Au@FeS-PEG) with strong NIR absorption property exhibited an excellent therapeutic function to overcome hypoxia-associated radiotherapy resistance by means of mild photothermal therapy-initiated enhancement of oxygen level in the tumor microenvironment [81]. Therefore, the efficiency of radiotherapy was enhanced and this treatment modality was then further combined with photothermal therapy using this multifunctional nanoparticles, resulting in more efficient treatment of **tumor hypoxia**.

Table 2. Recently developed magnetic gold nanocomposites for multi-therapy in cancer treatment.

	nanocomposite	cancer type	treatment modalities	achievement	ref.
Gold shell	Fe_3O_4@Au@mSiO_2-dsDNA/DOX	cervical	photothermal therapy/chemotherapy	synergistic effect of magnetic field and NIR light showed the significant therapeutic effect	[74]
	CDF-Au	cervical	photothermal therapy/chemotherapy	enhancement of selectivity and potentiality to overcome resistance to the anticancer drug	[75]
	MUA-PEG/SiNC/IOC-Au	breast	photothermal therapy/photodynamic therapy	improved the efficiency of combined therapy using external magnetic field	[76]
	Au@Fe_2O_3	head and neck	photothermal therapy/radiotherapy	combined therapy induced a large extent of apoptosis in cancer cell	[77]

Gold material	GNR@IOs-DOX	breast	photothermal therapy/chemotherapy	complete removal of the tumor without recurrence by magnetically tumor homing of the therapeutic agent and its synergistic effect	[78]
	pDNA/Au@PDM/Fe_3O_4	glioma	photothermal therapy/gene therapy	effective tumor inhibition through a combination of dual therapy	[79]
	BPs@Au@Fe_3O_4	cervical	photothermal therapy/photodynamic therapy	dual therapy using low power NIR light suppressed the tumor growth efficiently	[80]
	Au@FeS-PEG	breast	photothermal therapy/radiotherapy	enhancement of radiotherapy efficiency in hypoxic tumor microenvironment by mild photothermal therapy	[81]

Combined AuNPs-based approaches for theranostics

Theranostic agents have attracted major interest in recent years because of their concurrent diagnostic and therapeutic roles in biomedicine. In this regard, nanoparticle-based platforms have been identified as valid tools for cancer theranostics. Therefore, multifunctional magnetic AuNPs containing both magnetic and optical properties have been rapidly developed to achieve an effective theranostic agent, advantageous for multi-imaging and multi-therapy of cancer. Han and colleagues demonstrated that indocyanine green-loaded protein-stabilized gadolinium oxide-gold nanoclusters nanoplatform was more effective for multimodal imaging as mentioned in the previous section and this nanoplatform further improved PDT and PTT [66]. Drug-loaded nanocapsules (GNR@IOs-DOX) also allowed for the diagnosis of the tumor by MRI and PAI imaging techniques because of their magnetic and plasmonic properties [78]. Trimodal imaging (e.g., MRI, CT, and PAI) of the tumor using nanocomposite of AuNRs and IONPs having multiple therapeutic abilities was effective for cancer theranostic applications [79].

Additionally, several cancer theranostic agents composed of gold and magnetic materials have been reported through various types of combination such as single therapy with single imaging, single therapy with multi-imaging, and multi-therapy with single imaging. Peptide engineered metal-organic framework-based nanocomposites had longitudinal relaxivity of 1.204 mM^{-1} s^{-1} and highly stable photothermal conversion efficiency of 40.5% that are suitable for efficient T_1-weighted MRI and photothermal therapy, respectively [82]. Thus, this nanocomposite attained theranostic capacity specifically for triple-negative breast cancer. The core-shell theranostic nanoplatform composed of anticancer drug nanoparticles as a core and coated with a thin layer gold shell with magnetic IONPs was prepared to combine MRI and synergistic effects of PTT and chemotherapy [83]. Zhang research group developed γ-Fe_2O_3@Au core-shell magnetic gold nanoflowers-based cancer theranostics, which allowed the precise determination of the tumor by multi-imaging techniques including MRI, PAI, and SERS, as well as the efficient destruction of the tumor by PTT [84].

Biosafety of magnetic AuNPs

The **biosafety** evaluation of nanomaterials is essential for their safe clinical application in the biomedical field. The toxicity of nanomaterials depends on their size, shape, surface chemistry, biological target, and time of exposure [85]. Over the past decades, several *in vitro* and *in vivo* toxicity studies have been performed to demonstrate the lower toxicity of individual AuNPs and MNPs [86,87]. However, the complete understanding of the toxic effects of magnetic gold hybrids to biological systems is still limited.

The most recent studies aimed to elucidate the toxicological impact of magnetic AuNPs *in vitro* and *in vivo*, highlighted the safety profile of these nanocomplexes. The hybrid of gadolinium oxide-gold nanoclusters employed for multimodal imaging had negligible hemolytic effect at concentration range of 1.6-16 mg mL^{-1} and also cell viability remained above 80% using this hybrid at concentration as high as 8 mg mL^{-1} [66]. Multifunctional therapeutic agents Au@FeS induced no observable toxicity after 30 days post-injection to healthy mice at high dose of 20 mg kg^{-1} [81]. Furthermore, magnetic gold hybrids such as Fe_2O_3@Au exhibited no significant toxicity on healthy tissues including liver, heart, kidney, and lung [82,84]. As a result, these hybrids were successfully established as cancer theranostics agents in pre-clinical studies.

Concluding Remarks and Future Perspectives

Multifunctional nanomaterials have displayed more benefits in biomedicine owing to their effective synergistic diagnostic and therapeutic effects. In this review, we have summarized on the design, preparation and properties of magnetic gold multifunctional nanomaterials as cancer theranostics that support their utilization for simultaneous diagnosis using multiple imaging techniques as well as treatment using multiple therapeutic approaches. Recent pre-clinical studies showed that due to the versatile physiochemical properties of magnetic gold nanomaterials, their applications in multimodal imaging and therapy of tumors are more fruitful for cancer treatment compared to individual approaches by overcoming some of their previous limitations. Though several pre-clinical studies successfully demonstrated the higher theranostic efficiency of magnetic gold nanomaterials, nevertheless some important aspects should be considered for further improvement in theranostic outcome and successive clinical translation (see Outstanding Questions).

The magnetic gold nanocomposites possess both magnetic as well as optical properties and also these properties affect to each other depending on the nature of each material. Furthermore, the sensitivity and resolution of the various imaging techniques and the efficiency of therapies are usually different. As a result, the composition of nanocomposites is a crucial factor to regulate their physiochemical properties and later the efficiency of multimodal imaging and therapy. Therefore, the optimization of physiochemical properties of nanocomposites via tuning their size, shape, and appropriateness of the choice of nanomaterials is essential to enhance their performance.

Inorganic nanoparticles possess unique physical and chemical properties that are more suitable for imaging and therapeutic purpose, while these nanoparticles also exhibit toxicity effects to human healthy tissues and organs. Additionally, the toxicity depends on other parameters such as surface chemistry. In order to apply the multifunctional magnetic gold nanomaterials in the human body; their complete biosafety evaluation is mandatory by means of monitoring biodistribution, accumulation and clearance of these nanomaterials in healthy tissues and organs after successful applications. Moreover, to reduce the significant side effects in multimodal approaches that arise from additional imaging and therapeutic agents (e.g., radioactive elements and drug molecules) as well as external stimuli (e.g., high power laser and ionizing radiation) during and after cancer treatment, several issues should be carefully addressed. For instance, adjustment of

minimum essential doses of imaging and therapeutic agents, enhancement of desired properties of magnetic gold nanomaterials that allows therapeutic performance under biologically safe external stimuli and selection of less harmful imaging and therapeutic modalities without any major compromise in the efficiency of cancer treatment. We are confident that solving most of these issues will bring this advanced new class of colloidal nanomaterials to maturation for starting the transition toward a first in man study to the benefit of patients, society and the health care system.

Acknowledgments

This work was supported by AIRC (grant IG 2018, ID: 21565 to DP), Fondazione Regionale per la Ricerca Biomedica (FRRB), and Direzione Generale Ricerca, Innovazione, Università, Export e Internazionalizzazione of the Regione Lombardia.

References

1 Fan, W. *et al.* (2017) Nanotechnology for multimodal synergistic cancer therapy. *Chem. Rev.* 117, 13566–13638

2 Marangoni, V.S. *et al.* (2017) Enhancing T_1 magnetic resonance imaging contrast with internalized gadolinium(III) in a multilayer nanoparticle. *Proc. Natl. Acad. Sci. U. S. A.* 114, 6960-6965

3 Ge, Y. *et al.* (2018) Preparation and characterization of Fe_3O_4@Au-C225 composite targeted nanoparticles for MRI of human glioma. *PLoS One* 13, e0195703

4 Mahan, M.M. and Doiron, A.L. (2018) Gold nanoparticles as X-ray, CT, and multimodal imaging contrast agents: formulation, targeting, and methodology. *J. Nanomater*. 2018, 5837276

5 Li, Y. *et al.* (2018) Surface-enhanced Raman nanoparticles for tumor theranostics applications. *Acta Pharm. Sin. B* 8, 349-359

6 Li, W. and Chen, X. (2015) Gold nanoparticles for photoacoustic imaging. *Nanomedicine* 10, 299-320

7 Yao, C. *et al.* (2016) Gold nanoparticle mediated phototherapy for cancer. *J. Nanomater.* 2016, 5497136

8 Haume, K. *et al.* (2016) Gold nanoparticles for cancer radiotherapy: a review. *Cancer Nanotechnol*. 7, 8

9 Dreaden, E.C. *et al.* (2012) Size matters: gold nanoparticles in targeted cancer drug

delivery. *Ther. Deliv.* 3, 457-478

10 Ding, Y. *et al.* (2014) Gold nanoparticles for nucleic acid delivery. *Mol. Ther.* 22, 1075-1083

11 Gharatape, A. and Salehi, R. (2017) Recent progress in theranostic applications of hybrid gold nanoparticles. *Eur. J. Med. Chem*. 138, 221-233

12 Guo, J. *et al.* (2017) Gold nanoparticles enlighten the future of cancer theranostics. *Int. J. Nanomed*. 12, 6131-6152

13 Singh, P. *et al.* (2018) Gold nanoparticles in diagnostics and therapeutics for human cancer. *Int. J. Mol. Sci*. 19, 1979

14 Jin, Y. (2012) Engineering plasmonic gold nanostructures and metamaterials for biosensing and nanomedicine. *Adv. Mater.* 24, 5153-5165

15 Chen, L.Y. *et al.* (2015) Fluorescent gold nanoclusters: recent advances in sensing and imaging. *Anal. Chem.* 87, 216-229

16 Zhao, J.Y. *et al.* (2014) Cytotoxicity of nucleus-targeting fluorescent gold nanoclusters. *Nanoscale* 6, 13126-13134

17 Daniel, M.C. and Astruc, D. (2004) Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chem. Rev*. 104, 293-346

18 Zheng, Y. *et al.* (2014) Successive, seed-mediated growth for the synthesis of single-crystal gold nanospheres with uniform diameters controlled in the range of 5-150 nm. *Part. Part. Syst. Charact.* 31, 266-273

19 Brust, M. *et al.* (1994) Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid-liquid system. *J. Chem. Soc., Chem. Commun.* 0, 801-802

20 Huang, X. *et al.* (2009) Gold nanorods: from synthesis and properties to biological and biomedical applications. *Adv. Mater*. 21, 4880-4910

21 Wang, S. *et al.* (2015) Three-photon luminescence of gold nanorods and its applications for high contrast tissue and deep in vivo brain imaging. *Theranostics* 5, 251-266

22 Zhao, J. *et al.* (2014) Cancer theranostics with gold nanoshells. *Nanomedicine* 9, 2041-2057

23 Jin, Y. *et al.* (2010) Multifunctional nanoparticles as coupled contrast agents. *Nat. Commun.* 1, 41

24 Wang, H. *et al.* (2016) One–pot seedless synthesis of uniform gold nanoshells and their photothermal conversion property. *ChemistrySelect* 1, 659-663

25 Skrabalak, S.E. *et al.* (2008) Gold nanocages: synthesis, properties, and applications. *Acc. Chem. Res.* 41, 1587-1595

26 Avvakumova, S. *et al.* (2016) Theranostic nanocages for imaging and photothermal therapy of prostate cancer cells by active targeting of neuropeptide-Y receptor. *Bioconjugate Chem.* 27, 2911-2922

27 Grzelczak, M. *et al.* (2008) Shape control in gold nanoparticle synthesis. *Chem. Soc. Rev*. 37, 1783-1791

28 Chen, L. *et al.* (2014) High-yield seedless synthesis of triangular gold nanoplates through oxidative etching. *Nano Lett.* 14, 7201-7206

29 Barbosa, S. *et al.* (2010) Tuning size and sensing properties in colloidal gold nanostars. *Langmuir* 26, 14943-14950

30 Minami, T. *et al.* (2010) Shape-controllable gold nanocrystallization using an amphiphilic polythiophene. *Chem. Commun.* 46, 8603-8605

31 Choi, K.W. *et al.* (2013) Robust synthesis of gold rhombic dodecahedra with well-controlled sizes and their optical properties. *CrystEngComm* 15, 252-258

32 Das, P. *et al.* (2019) Recent advances in magnetic fluid hyperthermia for cancer therapy. *Colloids Surf., B* 174, 42-55

33 Reguera, J. *et al.* (2016) Synthesis of Janus plasmonic-magnetic, star-sphere nanoparticles, and their application in SERS detection. *Faraday Discuss.*191, 47-59

34 Reguera, J. *et al.* (2017) Janus plasmonic-magnetic gold-iron oxide nanoparticles as contrast agents for multimodal imaging. *Nanoscale* 9, 9467-9480

35 Efremova, M.V. *et al.* (2018) Magnetite-gold nanohybrids as ideal all-in-one platforms for theranostics. *Sci. Rep.* 8, 11295

36 Xuan, S. *et al.* (2009) Preparation, characterization, and catalytic activity of core/shell Fe_3O_4@polyaniline@Au nanocomposites. *Langmuir* 25, 11835-11843

37 Lee, M. *et al.* (2015) Preparation of plasmonic magnetic nanoparticles and their light scattering properties. *RSC Adv.* 5, 21050-21053

38 Abbas, M. *et al.* (2017) Multifunctional Fe_3O_4/Au core/satellite nanocubes: an efficient chemical synthesis, characterization and functionalization of streptavidin protein. *Dalton Trans.* 46, 2303-2309

39 Zhang, M. *et al.* (2013) Preparation, characterization and catalytic activity of core-satellite Au/Pdop/SiO_2/Fe_3O_4 magnetic nanocomposites. *RSC Adv.* 3, 13818-13824

40 Smolensky, E.D. *et al.* (2011) Fe_3O_4@organic@Au: core-shell nanocomposites with high saturation magnetisation as magnetoplasmonic MRI contrast agents. *Chem.*

Commun. 47, 2149-2151

41 Wang, J. *et al.* (2016) Facile synthesis of Au-coated magnetic nanoparticles and their application in bacteria detection via a SERS method. *ACS Appl. Mater. Interfaces* 8, 19958-19967

42 Kwizera, E.A. *et al.* (2016) Size- and shape-controlled synthesis and properties of magnetic-plasmonic core-shell nanoparticles. *J. Phys. Chem. C* 120, 10530-10546

43 Chen, Z.Y. *et al.* (2014) Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. *BioMed Res. Int*. 2014, 819324

44 Chen, K.L. *et al.* (2016) Influence of magnetoplasmonic γ-Fe_2O_3/Au core/shell nanoparticles on low-field nuclear magnetic resonance. *Sci. Rep.* 6, 35477

45 Wang, H. *et al.* (2016) High sensitivity of gold nanoparticles co-doped with Gd_2O_3 mesoporous silica nanocomposite to nasopharyngeal carcinoma cells. *Sci. Rep.* 6, 34367

46 Rotz, M.W. *et al.* (2015) High relaxivity Gd(III)-DNA gold nanostars: investigation of shape effects on proton relaxation. *ACS Nano* 9, 3385-3396

47 Holbrook, R.J. *et al.* (2016) Gd(III)-dithiolane gold nanoparticles for T_1-weighted magnetic resonance imaging of the pancreas. *Nano Lett.* 16, 3202-3209

48 Sabale, S. *et al.* (2017) Recent developments in the synthesis, properties, and biomedical applications of core/shell superparamagnetic iron oxide nanoparticles with gold. *Biomater. Sci*. 5, 2212-2225

49 Wang, G. *et al.* (2016) Au nanocage functionalized with ultra-small Fe_3O_4 nanoparticles for targeting T_1-T_2 dual MRI and CT imaging of tumor. *Sci. Rep.* 6, 28258

50 Kim, D.H. *et al.* (2016) Multimodal imaging of nanocomposite microspheres for transcatheter intra-arterial drug delivery to liver tumors. *Sci. Rep.* 6, 29653

51 Chen, P.J. *et al.* (2015) Multitheragnostic multi-GNRs crystal-seeded magnetic nanoseaurchin for enhanced in vivo mesenchymal-stem-cell homing, multimodal imaging, and stroke therapy. *Adv. Mater.* 27, 6488-6495

52 Pan, D. *et al.* (2013) A brief account of nanoparticle contrast agents for photoacoustic imaging. *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* 5, 517-543

53 Yang, H.W. *et al.* (2013) Magnetic gold-nanorod/ PNIPAAmMA nanoparticles for dual magnetic resonance and photoacoustic imaging and targeted photothermal therapy. *Biomaterials* 34, 5651-5660

54 Zhao, C. *et al.* (2016) Biosynthesized gold nanoclusters and iron complexes as scaffolds for multimodal cancer bioimaging. *Small* 12, 6255-6265
55 Denk, W. *et al.* (1990) Two-photon laser scanning fluorescence microscopy. *Science* 248, 73-76
56 Li, M. *et al.* (2016) Core-shell nanostars for multimodal therapy and imaging. *Theranostics* 6, 2306-2313
57 Jin, X. *et al.* (2014) Multifunctional superparamagnetic nanoshells: combining two-photon luminescence imaging, surface-enhanced Raman scattering and magnetic separation. *Nanoscale* 6, 14360-14370
58 Zhou, Y.M. *et al.* (2013) Yolk-type Au@Fe_3O_4@C nanospheres for drug delivery, MRI and two-photon fluorescence imaging. *Dalton Trans.* 42, 9906-9913
59 Palonpon, A.F. *et al.* (2013) Raman and SERS microscopy for molecular imaging of live cells. *Nat. Protoc.* 8, 677-692
60 Amendola, V. *et al.* (2014) Magneto-plasmonic Au-Fe alloy nanoparticles designed for multimodal SERS-MRI-CT imaging. *Small* 10, 2476-2486
61 You, Q. *et al.* (2017) BSA-bioinspired gadolinium hybrid-functionalized hollow gold nanoshells for NIRF/PA/CT/MR quadmodal diagnostic imaging-guided photothermal/photodynamic cancer therapy. *ACS Appl. Mater. Interfaces* 9, 40017-40030
62 Eyvazzadeh, N. *et al.* (2017) Gold-coated magnetic nanoparticle as a nanotheranostic agent for magnetic resonance imaging and photothermal therapy of cancer. *Lasers Med. Sci.* 32, 1469-1477
63 Ngwa, W. *et al.* (2014) Targeted radiotherapy with gold nanoparticles: current status and future perspectives. *Nanomedicine* 9, 1063-1082
64 Yang, Y. *et al.* (2016) Tumor angiogenesis targeted radiosensitization therapy using gold nanoprobes guided by MRI/SPECT imaging. *ACS Appl. Mater. Interfaces* 8, 1718-1732
65 Brown, S.B. *et al.* (2004) The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol*. 5, 497-508
66 Han, L. *et al.* (2017) Protein-stabilized gadolinium oxide-gold nanoclusters hybrid for multimodal imaging and drug delivery. *ACS Appl. Mater. Interfaces* 9, 6941-6949
67 Kwon, K.C. *et al.* (2017) Superparamagnetic gold nanoparticles synthesized on protein particle scaffolds for cancer theragnosis. *Adv. Mater.* 29, 1701146
68 DeVita, V.T. and Chu, E. (2008) A history of cancer chemotherapy. *Cancer Res*. 68,

8643-8653

69 Mody, V.V. *et al.* (2014) Magnetic nanoparticle drug delivery systems for targeting tumor. *Appl. Nanosci.* 4, 385-392

70 Peng, J.R. *et al.* (2014) Mesoporous magnetic gold "nanoclusters" as theranostic carrier for chemo-photothermal co-therapy of breast cancer. *Theranostics* 4, 678-692

71 Louie, A. (2010) Multimodality imaging probes: design and challenges. *Chem. Rev.* 110, 3146-3195

72 Wu, X. *et al.* (2014) Silica-encapsulated Gd^{3+}-aggregated gold nanoclusters for in vitro and in vivo multimodal cancer imaging. *Chem. Eur. J.* 20, 8876-8882

73 Wang, W. *et al.* (2018) Spiky Fe_3O_4@Au supraparticles for multimodal in vivo imaging. *Adv. Funct. Mater.* 28, 1800310

74 Li, W.P. *et al.* (2014) Formation of oligonucleotide-gated silica shell-coated Fe_3O_4-Au core-shell nanotrisoctahedra for magnetically targeted and near-infrared light-responsive theranostic platform. *J. Am. Chem. Soc.* 136, 10062-10075

75 Ma, Y. *et al.* (2013) Gold nanoshell nanomicelles for potential magnetic resonance imaging, light-triggered drug release, and photothermal therapy. *Adv. Funct. Mater.* 23, 815-822

76 Bhana, S. *et al.* (2015) Near-infrared-absorbing gold nanopopcorns with iron oxide cluster core for magnetically amplified photothermal and photodynamic cancer therapy. *ACS Appl. Mater. Interfaces* 7, 11637-11647

77 Hosseini, V. *et al.* (2018) Multimodal cancer cell therapy using Au@Fe_2O_3 core–shell nanoparticles in combination with photo-thermo-radiotherapy. *Photodiagn. Photodyn. Ther.* 24, 129-135

78 Huang, L. *et al.* (2016) Magneto-plasmonic nanocapsules for multimodal-imaging and magnetically guided combination cancer therapy. *Chem. Mater.* 28, 5896-5904

79 Hu, Y. *et al.* (2016) Multifunctional pDNA-conjugated polycationic Au nanorod-coated Fe_3O_4 hierarchical nanocomposites for trimodal imaging and combined photothermal/gene therapy. *Small* 12, 2459-2468

80 Yang, D. *et al.* (2017) Assembly of Au plasmonic photothermal agent and iron oxide nanoparticles on ultrathin black phosphorus for targeted photothermal and photodynamic cancer therapy. *Adv. Funct. Mater.* 27, 1700371

81 Chen, J. *et al.* (2017) Synergistic effect of thermo-radiotherapy using Au@FeS core–shell nanoparticles as multifunctional therapeutic nanoagents. *Part. Part. Syst.*

Charact. 34, 1600330

82 Zhang, L. *et al.* (2018) ZD2-engineered gold nanostar@metal-organic framework nanoprobes for T_1-weighted magnetic resonance imaging and photothermal therapy specifically toward triple-negative breast cancer. *Adv. Healthcare Mater.* 1801144

83 Nan, X. *et al.* (2017) Dual-targeted multifunctional nanoparticles for magnetic resonance imaging guided cancer diagnosis and therapy. *ACS Appl. Mater. Interfaces* 9, 9986-9995

84 Huang, J. *et al.* (2015) Rational design and synthesis of Fe_2O_3@Au magnetic gold nanoflowers for efficient cancer theranostics. *Adv. Mater.* 27, 5049-5056

85 Sukhanova, A. *et al.* (2018) Dependence of nanoparticle toxicity on their physical and chemical properties. *Nanoscale Res. Lett*. 13, 44

86 Lewinski, N. *et al.* (2008) Cytotoxicity of nanopartides. *Small* 4, 26-49

87 Yildirimer, L. *et al.* (2011) Toxicology and clinical potential of nanoparticles. *Nano Today* 6, 585-607

Glossary

Biosafety: the inhibition of loss of biological integrity in large scale due to nanomaterials effect on human health. Human biosafety of nanomedicine is a major concern for clinical use.

Cancer disease: a large number of diseases that involves abnormal cell proliferation and the ability to spread throughout the body. Cancer is the third leading cause of death in the world.

Clinical translation: a research leads to superior development of new diagnostic and therapeutic approaches by way of measuring their impact in the human body.

Localized surface plasmon resonance: a unique optical characteristic of conductive nanomaterials produced by incident light-driven collective oscillation of conduction band electrons in nanomaterials of a size smaller than the wavelength of light. It is a powerful analytical technique in biomarkers determination as well as useful for photothermal therapy.

Magnetic gold: a type of nanocomposites composed of gold nanomaterials and magnetic materials shows the inherent properties of both materials.

Multifunctional nanomaterial: an innovative nanoplatform in biomedicine that exhibits multiple functions to determine and treatment of diseases by acting as contrast agents and therapeutic agents for various imaging and therapy. Multifunctional nanoparticles are more effective for cancer management.

Multimodal approach: most effective approach in biomedical field consists of more than one diagnostic and therapeutic approach in order to precise identification as well as enhanced treatment of diseases.

Nanocomposites: high-performance nanomaterials made of two or more materials that display properties of typical properties of individual material.

Nanostructures: a material of different dimensions with size in the range of nanometer scale.

Non-invasive technique: a conventional medical technique that does not involve incision into the body or the removal of tissue during diagnosis as well as treatment.

Photoacoustic imaging: photoacoustic effect based an emerging biomedical imaging modality that has high prospective in preclinical research and clinical practice.

Photothermal therapy: a physiochemical therapy for cancer treatment in which released heat from photothermal agents (e.g., AuNPs) with high photothermal conversion efficiency under NIR laser irradiation kill cancer cells.

Radiotherapy: a therapeutic approach using a high dose of ionizing radiation to destroy cancer cells and shrink the tumors subsequently with limited side effects and high success rate.

Radiosensitizer: an agent including gold nanomaterials that archives greater tumor inhibition by amplification of X-ray radiation doses.

Theranostic: a new field of medicine in which simultaneous diagnosis and therapy are performed for the management of diseases.

Tumor hypoxia: a state of solid tumors arises from an insufficient supply of oxygen in blood vessels that leads to resistance to radiotherapy as well as chemotherapy.

Tumor microenvironment: the cellular environment where the tumor cells are surrounded by non-cancerous cells including fibroblasts, immune cells, proteins, and blood

vessels. The tumor can alteration this environment while the environment can affect the growth of the tumor.

Outstanding Questions

What is the role of size, shape, and composition of each material in nanocomposites to develop a novel cancer theranostics with optimum magnetic and optical properties for effective cancer diagnosis and treatment?

How to minimize the intrinsic toxicity of nanomaterials and side effects of an overdose of therapeutic agents and external stimuli to healthy tissues and organs?

Why do the unique magnetic and optical properties of magnetic gold nanomaterials allow for enhanced multiple imaging and therapy?

How many imaging and therapeutic modalities are needed for the development of multimodal cancer theranostic for the sensitive and selective early detection of cancer and also effective treatment of cancer including drug-resistant, hypoxic and metastatic tumor without any recurrence?

How can we modify the surface of magnetic gold nanomaterials with various agents (e.g., imaging, therapeutic, targeting and stabilizing) of appropriate ratios to get highly colloidal stable and biocompatible multifunctional magnetic gold nanomaterials for targeted cancer therapy in the clinic?

Highlights

Fundamental strategies for the synthesis of gold nanostructures with desirable optical properties are well developed, which is mandatory requirement for the design and fabrication of multifunctional magnetic gold nanomaterials.

Use of magnetic gold nanomaterials as contrast agent in multimodal imaging overcome the limitations of each individual imaging technique in early stage cancer diagnosis by providing enhanced spatial resolution and improved sensitivity.

Synergistic effects of multiple therapies using magnetic gold nanomaterials based therapeutic agent are more effective in the treatment of cancer compared to single therapy.

Cancer theranostics based on a combination of multiple imaging and therapies show excessive potentiality to fight against cancer, in which biocompatible multifunctional magnetic gold nanomaterials can play a significant role in clinical translation in the future.

Figure 1

Click here to access/download;Figure;Figure 1.tif

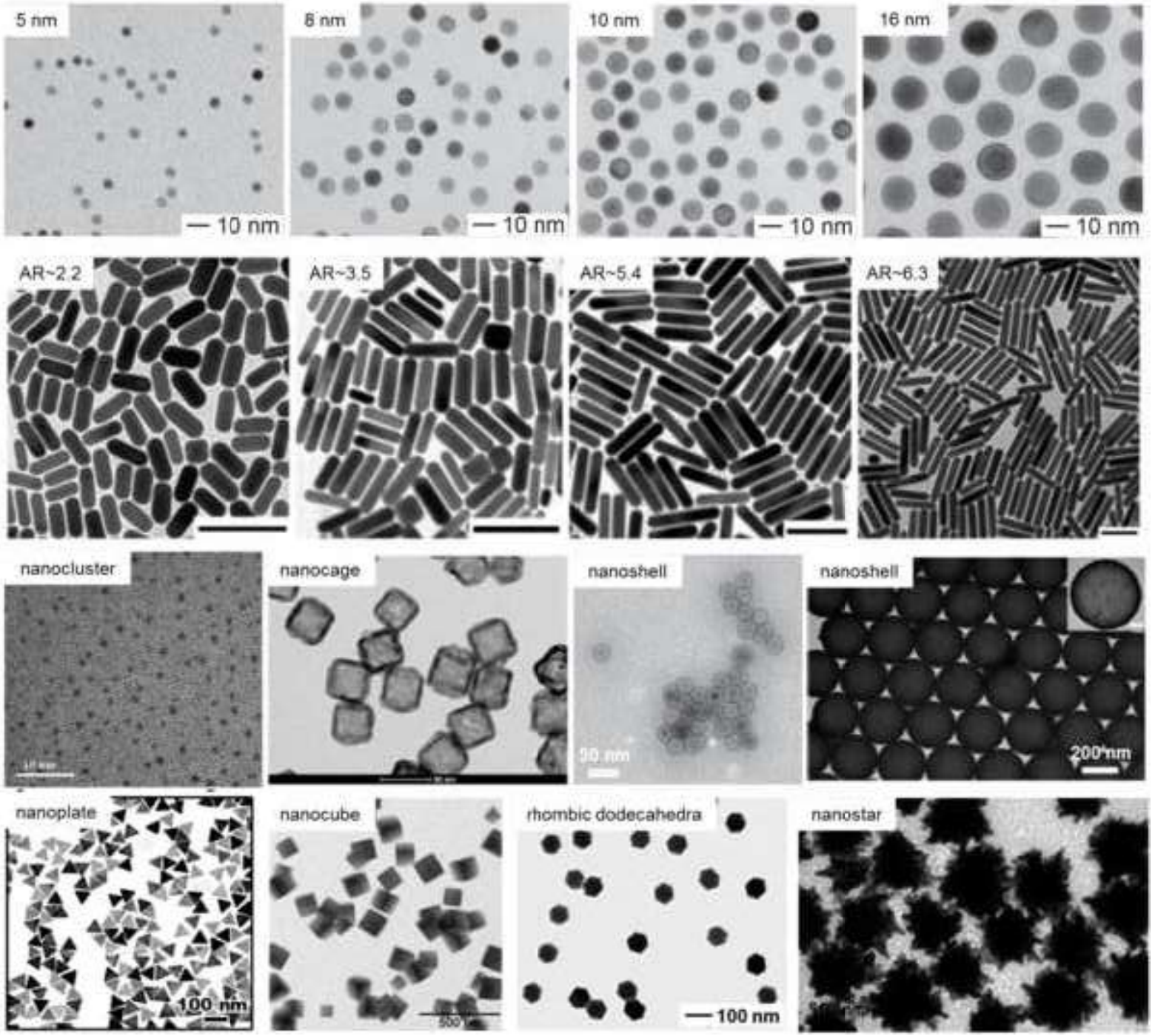
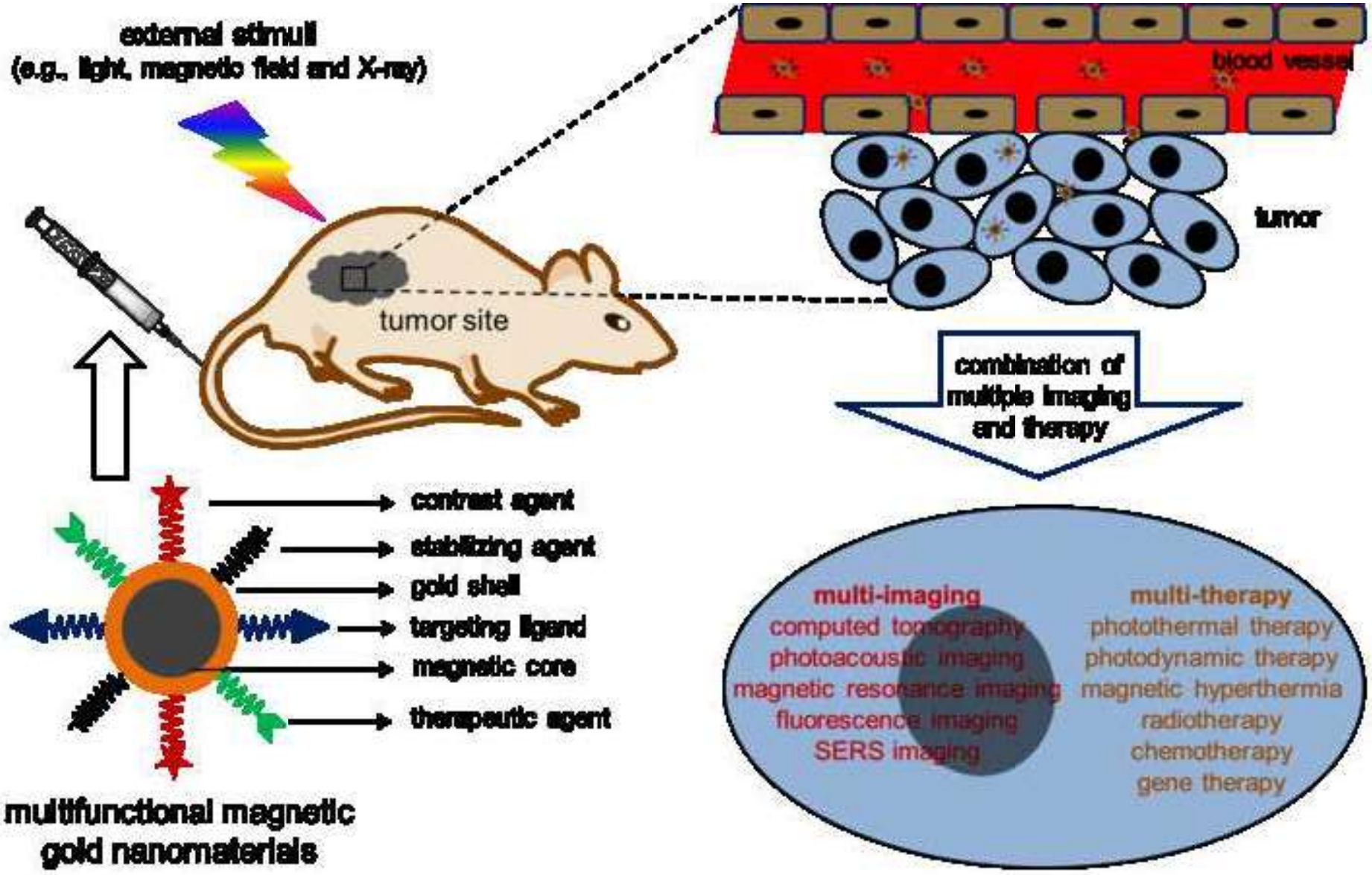


Figure 2

Click here to access/download;Figure;Figure 2.tif



Box Figure

Click here to access/download;Figure;Figure I.tif