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Review

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Latest advances in combining gold nanomaterials with physical stimuli towards new responsive therapeutic and diagnostic strategies

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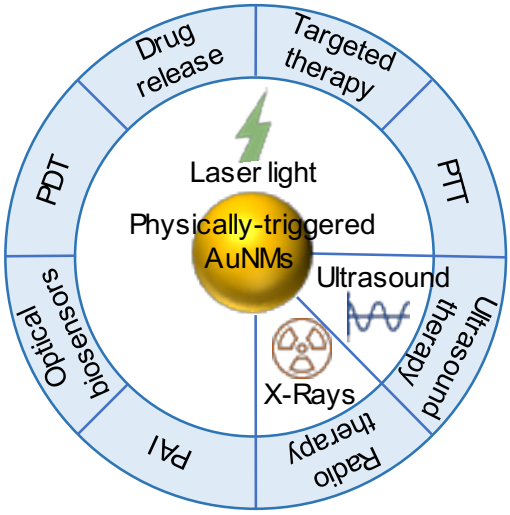
Graphical abstract



Keywords

Gold nanoparticle[1]; external stimuli; physical stimuli; physically triggered nanomedicine.

Abstract

Nanomedicine aims at enhancing treatment efficiency and/or improving diagnostic sensitivity by better controlling several critical parameters, such as tissue targeting and off-target toxicity. More recently, advanced nanomedicine products have been developed to achieve spatially and temporally controlled therapy and diagnosis. This review focuses on gold nanomaterials (AuNMs) and alloy/hybrid AuNMs that can be used in stimuli-responsive strategies for therapeutic and diagnostic applications. Endogenous and/or exogenous stimuli can be used as a trigger for such systems. Herein, we focus on those activated by exogenous stimuli. Our review starts from one specific externally activated product, Aurolase®, which recently underwent clinical studies. Further we continue describing a specific physically triggered category, for which the exogeneous stimulus applied induces a structural transformation or modification that is essential for their therapeutic and/or diagnostic action. Gold nanomaterials are grouped both by the nature of the function they exert (therapeutic or diagnostic) and the stimuli class.

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[1] In this review we will refer to nanomaterials without detailing their geometrical shapes since those of secondary importance to the scope of the review.

Rationale and Purpose

In the last decades, the growing incidence of chronic diseases associated with the increased aging of the population has triggered the need for more effective and localized therapies as well as efficient diagnostic tools for early disease detection. AuNMs and alloy/hybrid AuNMs have been widely investigated to address this need. The gold nanomaterials reviewed herein constitute the most advanced research on this promising technology.

This review focuses on those AuNMs and alloy/hybrid AuNMs activated by externally applied physical stimuli.

Introduction

Clinical translation of AuNMs to date

Gold nanomaterials (AuNMs) and alloy/hybrid AuNMs offer a valuable platform for a wide range of biomedical applications, ranging from therapy to diagnosis [1, 2].

Furthermore, both AuNMs and alloy/hybrid AuNMs provide excellent platforms to develop multifunctional approaches ("theragnostics") [3-5]. As compared to gold nanomaterials, alloy or hybrid AuNMs offer the added advantage of combining the unique properties of multiple components within a single product. Alloy AuNMs incorporate inorganic components (e.g., iron oxide [6, 7]); whereas, hybrid AuNMs integrate a gold core within organic nanostructures (polymeric nanoparticles [8], liposomes, dendrimers, micelles or biomacromolecules [9]). Owing to their composition, alloy and hybrid AuNMs provide excellent platforms to develop theragnostic tools, where the nanomaterial is used as diagnosis probe and therapeutic agent at the same time.

Various gold and alloy/hybrid gold nanoparticles are currently under investigation in clinical studies for their application as therapeutic and/or diagnostic tools (Table 1). However, no AuNM has reached clinical approval for therapeutic applications [10-12]. Conversely, examples of FDA-approved, AuNM-based diagnostics can be found, such as the Uni-Gold Recombigen HIV-1/2, a single-use rapid immunoassay for the qualitative detection of antibodies to human immunodeficiency virus (HIV)-1 and/or HIV-2 in human serum, plasma, and whole blood [13]; the VERIGENE® system, for the detection of DNA, RNA or protein targets; the First Response Gold Digital Pregnancy Test [14]; and the Single Path *E. Coli* O157 Gold Labelled Immunosorbent Assay, used in food analysis laboratories. All these diagnostic tests fall under the optical biosensor category, where AuNMs are used as labels for signal amplification in bio-recognizing events

AuNMs and alloy/hybrid AuNMs can be finely tuned so that their therapeutic effect or diagnostic action is triggered by specific stimuli [15-17]. Stimuli can be associated with specific biological (endogenous) factors, such as the microenvironmental properties of a defined diseased condition (e.g., acidic pH [18] and levels of reductive agents [19] in the tumour tissue, or intracellular enzymatic activity [20]). These are the so-called "internal stimuli" or "intrinsic stimuli" and are generally associated with disease progression. Alternatively, AuNMs can be designed to respond to externally applied physical stimuli ("external stimuli" or "exogeneous stimuli"): examples include, but are not limited to, light, temperature, magnetic and electric field, and X-rays. As compared to internal triggers, external stimuli are easier to control, are not associated with a patient- or disease-dependant variability and can be selected based on key parameters like cost and safety.

Aurolase® Therapy – An example of physical stimuli-triggered AuNMs from the clinics

Among the AuNMs under clinical development listed in Table 1, the Aurolase® therapy is of particular interest for this review, as it is a unique example of a stimuli responsive AuNM that has been translated from the lab bench to the clinic. No other stimuli-responsive, AuNM-based therapy has entered clinical trials yet. Similarly, no clinical example can be found of on/off AuNM switch probes that exert their detection function by responding to a physical stimulus. Diagnostic AuNM-based tools that have reached regulatory approval or are in a clinical trial to date act as signals enhancers.

Table 1. Ongoing clinical studies on gold and gold alloy/hybrid nanomaterials found on clinicaltrials.gov (last updated: February 2020).

Application		Product name	Product type	Condition or disease	Clinical study phase	ClinicalTrials.gov Identifier
Therapy	Drug delivery	NU-0129	SNA bound on spherical AuNPs	Gliosarcoma Recurrent glioblastoma	Early Phase 1	NCT03020017
		C19-A3 GNP (also known as MTX 102)	Intradermal micro-injectable solution of human C19A3 proinsulin peptide coupled to carbohydrate-coated gold nanoparticles	Type 1 diabetes	Phase 1	NCT02837094
	Induce re-myelination	CNM-Au8	Gold nanocrystals	Chronic optic neuropathy in multiple sclerosis	Phase 2	NCT03536559
				Parkinson's disease	Phase 2	NCT03815916
	Photo-thermal ablation therapy	AuroLase® Therapy	Auroshells® (silica nanoparticles with a gold shell)	Prostate neoplasm	N/A	NCT02680535
						NCT04240639
	Cavity surface pre-treatment	Nano Care Gold	Mixture of AuNPs and AgNPs suspended in 70 % isopropyl alcohol	Caries	N/A	NCT03669224
Diagnosis	Contrast agent	SEB-250	Silica nanoparticles surrounded by a shell of gold	Acne vulgaris	N/A	NCT03573115
	Artificial nose	AuNPs	Cross-reactive AuNPs coated with organic ligands	Pulmonary arterial hypertension	N/A	NCT02782026

The clinical study phase is indicated as “not applicable” when referring to studies without FDA-defined phases, such as trials of medical devices. Only active clinical trials are listed; completed or terminated clinical trials are not reported.

Abbreviations: AgNPs = silver nanoparticles; AuNPs = gold nanoparticles; SNA = spherical nucleic acid.

The Aurolase® product, developed by Nanospectra, is based on the use of silica-gold nanoshells, called Auroshells™, coated with (poly)ethylene glycol (PEG) and with sizes between 140 and 150 nm. Auroshells™ are designed to thermally ablate the solid tumors following stimulation with a NIR high-power diode source as external stimuli [21-23].

At the pre-clinical stage, Auroshells™-mediated photothermal therapy has been reported to improve the overall survival in various cancer models, including for example a murine xenograft model of glioma [24] and an

orthotopic canine model of a brain tumor [25]. The safety profile for the intravenous administration of Auroshells™ was proven in vitro [26], in vivo, [26] and patients with human prostate cancer [27]. Once intravenously administered, progressive extravasation and accumulation of Auroshells™ was demonstrated at the tumor site [28], associated with the enhanced permeation and retention (EPR) effect [28, 29]. In this context, human data showed that the clinical use of Aurolase® therapy has one main limitation: the EPR-driven accumulation of the Auroshells™ is heterogeneous within tumor tissues. The EPR effect is a passive targeting mechanism [29] that refers to the preferential accumulation and site-specific delivery of nanomaterials in the perivascular tumor region, due to the leakiness of the tumor vasculature and poor lymphatic drainage [30]. Briefly, systemically administered nanomaterials cross the tumor vascular barrier through intercellular gaps, are retained within the tumor tissue owing to the pressure created by poor lymphatic drainage, and penetrate by convection [31] through the tumor stroma to reach the cancer cells [32]. However, the tumor vasculature is characterized by abnormal angiogenesis, which leads a heterogeneous vessel network formation and, subsequently, tumor areas where the vasculature is completely lacking [33]. This, along with the high interstitial pressure and the mechanical stresses generated by the interactions between cancer/stromal cells and the extracellular matrix, lead to a heterogeneous EPR effect that negatively affects nanoparticle accumulation in the tumor [33]. Furthermore, large (> 50 nm in size) nanoparticles such as Auroshells™ have been shown to poorly penetrate dense tumor stroma [33]. The clinical consequence is that the highest Auroshells™ doses are achieved in the tumor cortex, while almost no accumulation is detectable within the necrotic tumor core [28].

In a first clinical trial (NCT00848042), the AuroLase® therapy was used in the treatment of patients with refractory and/or recurrent tumors of the head and neck. Three treatment groups of five patients each were enrolled and observed for six months following treatment. Each group received a single dose of AuroShells™ followed by one or more interstitial illuminations with a NIR laser. Particle dose and laser power differed among groups: the AuroShells™ doses tested were equal to 4.5 and 7.5 mL/Kg; whereas, laser power ranged between 3.5 to 5 watts. The therapy was shown not to be particularly safe, with serious and other side effects developed by many patients and attributable to the administration of the nanoparticles (NCT00848042). A second trial (NCT01679470) tested the efficacy of AuroLase® therapy for the localized treatment of primary or metastatic lung tumors with airway obstruction. NIR irradiation was delivered by optical fibre via bronchoscopy. This trial was, however, terminated. The most recent trial (NCT04240639), posted in January 2020 and currently recruiting patients, uses AuroShells™ as a contrast agent for magnetic resonance imaging (MRI), coupled to real-time transrectal ultrasound (US) to direct nanoparticles-triggered focal ablation of prostate neoplasms using NIR laser irradiation generated by means an FDA-approved laser and an interstitial optical fiber diffuser. This trial was approved based on very promising in vitro [34] and in vivo [35] data. According to the trial design, up to sixty prostate cancer patients will be recruited and will receive a single intravenous infusion of AuroShells™ 12 to 36 hours before MRI/US-guided laser irradiation. Tumor ablation will be assessed: (i) by contrast-enhanced MRI at 48 to 96 hours after laser illumination; (ii) by MRI/US-guided target biopsy at 6 months after laser treatment; and (iii) MRI/US-guided target biopsy in combination with standard biopsy after 1 year. NCT04240639 trial is expected to be completed by June 2023.

Discussion

As mentioned above, Aurolase® therapy is the sole stimuli responsive AuNM that has been translated from the lab bench to the clinic. Nevertheless, the scientific literature includes many other examples of AuNMs that respond to stimuli. Recently, a review by Tian et al. [16] reported on the main externally-stimulated AuNMs products that are at the early-stage development phases. Our review focuses instead on the means of external physical stimuli that can be employed in combination with AuNMs, and how these stimuli can induce modifications in the nanomaterial structure to trigger a therapeutic or diagnostic action, as the most advanced research on this promising

technology. Modifications in the nanomaterial structure include both chemical and physical changes, such as, for example, light-induced cleavage of photosensitive chemical bonds for spatial- and temporal-controlled drug release, melting of thermoresponsive coating polymers and subsequent targeted drug release, and nanomaterial phase transitions or polymer degradation in response to ultrasound stimulus. For more details on the design strategies that can be used for programming physical stimuli-responsive nanomaterials, a comprehensive review has been recently published by Sahle et al. [36].

The following sections discuss the types of external stimuli that can cause structural modifications in AuNMs, and how these chemical or physical modifications can be used for both therapeutic and diagnostic applications.

Types of triggers for stimuli responsive AuNMs

Non-ionizing radiations as external physical stimuli

Laser light

Laser light is the most common non-ionizing radiation used as external stimuli for AuNMs and alloy/hybrid AuNMs. Light is characterized by clinical relevance, excellent spatio-temporal controllability and indeed clinical safety. Its use is associated with AuNMs ability to efficiently absorb light, a property that results from the localized surface plasmon resonance (LSPR) effect. When administering light at a frequency that overlaps with the LSPR absorption, this is efficiently scattered generating both linear and nonlinear (e.g., third-harmonic generation) optical processes [37]. The remaining part of the energy is absorbed and dissipated into heat, through a rapid photothermal conversion by electron-phonon interaction [38, 39]. Photothermal conversion can lead not only to temperature increase but also to the generation of US waves and acoustic cavitation [39].

Targeting and functionalization strategies do not affect the photo-induced behaviour of AuNMs, enabling the multimodal/theragnostic applications of physical stimuli-triggered gold nanomaterials. On the other hand, the LSPR wavelength is influenced by several AuNM properties, including nanomaterial size, shape, structure, composition and the dielectric constant of the surrounding medium [40]. Increases in AuNMs size and aspect ratio, for example, result in a plasmonic resonance shift from an ultraviolet (UV)-visible range (400–520 nm) to the near-infrared (NIR) region (800–1200 nm) [16, 39]. For maximizing the effect of the physical stimulus, the laser light wavelength should be selected so that to match that of the LSPR band. Thus, the possibility to tune the LSPR of AuNMs towards the NIR light window is extremely advantageous, as tissues and biological fluids are moderately transparent in such spectral region, commonly known as "water window." In theory, UV light can also be employed as a physical stimulus, but it is associated with a limited ability to reach deep-seated tissues within the body. In general, small spherical AuNMs have higher photothermal conversion efficiency than those with larger diameters [41]. Furthermore, non-spherical AuNMs, including nanorods and nanostars, are more efficient than spherical AuNMs in producing heat following light stimuli, due to their larger absorption cross sections [42].

Temperature

Changes in temperature are used as an external stimulus to induce phase transitions in a controlled manner. Temperature-responsive systems are mainly hybrid AuNMs, where the gold core is coupled to a thermoresponsive polymer, such as poly(N-substituted acrylamide)s or poly(N-isopropylacrylamide-co-2-(dimethylamino)-ethylmethacrylate) [43]. Coupling is obtained via copolymerization, conjugation and/or grafting [36]. The intensity of the temperature stimulus needed to trigger a response, therefore, depends on the polymer type used and is independent of the AuNM physico-chemical properties.

Electric pulse and electric field

Electric waves are another external stimulus that can be used to activate the AuNMs therapeutic action. Electrical stimuli are relatively easy to generate, control, and remotely apply without the need for sophisticated instruments, which makes electro-responsive AuNMs a very attractive system.

Electric waves can be used to generate electroporation, where electrical pulses have been employed, for example, to achieve gene release from electro-responsive AuNMs in

animal models [44]. Electric waves can also generate an electric field, which triggers local heating of AuNMs [45, 46]. Because of differences in the characteristics of the AuNMs tested so far, the research community has not reached a consensus on the mechanism determining AuNM heat generation using an electric field. Nevertheless, two parameters have been identified as critical: electric field source and AuNMs properties, including size, concentration, and aggregation [47].

Ultrasound (US)

US waves are sound waves with frequencies higher than the upper audible limit of human hearing. US has been utilized as an exogenous stimulus for biomedical applications due to its non-invasiveness, ease of accessibility, cost-effectiveness, lack of ionizing radiation residues, controllable spatio-temporal effect, and high patient acceptability.

AuNMs can be activated by US waves in two ways [48]. They can be used together with sensitizing agents [49, 50], to prolong the non-radiative relaxation time of the sensitizer, thus promoting the generation of singlet oxygen. AuNMs can also act as nanosensitizers themselves [51, 52]. In the latter case, AuNMs act by enhancing the inertial cavitation rate in the biological tissue [53-55].

Magnetic field

Magnetic fields have long been investigated as an external stimulus for magnetic nanoparticles. However, AuNMs are not magnetic. In 2008, the concept of "super atom" has been used for the first time to indicate the extraordinary ferromagnetic and paramagnetic properties of small gold clusters [56]. These properties were then further described by other groups in the following years [57-59]. A current hypothesis explaining the mechanism by which AuNMs show magnetic properties is still controversial and has been extensively discussed elsewhere [60, 61]. However, applications of gold clusters for therapeutic hyperthermia under alternative magnetic force exposure have not been developed yet [62]. On the other hand, alloy iron oxide-gold nanoparticles have been investigated as contrast agents for MRI by exploiting the magnetic properties of iron oxide [63-67]. Magnetic alloy AuNMs and their biomedical applications have been comprehensively described in a recent review [68].

Ionizing radiations as external physical stimuli

X-rays

Gold is a high-Z element (Z=79) that has been widely used as radiosensitizers owing to its good absorption of ionizing radiations. Radiosensitization induces reactive oxygen species (ROS) production, increases oxidative stress, and promotes DNA damage in the targeted tissue by chemical interactions.

Like gold, AuNMs can be used to improve radiosensitivity [69]. The most famous example of AuNMs-based radiosensitizer is AuroVist™, a commercially available product for in vivo and in vitro research. In AuNMs radiosensitizers, the incident X-ray wave interacts with the nanoparticles, resulting in the emission of secondary electrons. Such electrons cause cell damage by direct interaction ("physical enhancement"), production of free radicals ("chemical enhancement"), and/or production of ROS and oxidative stress ("biological enhancement"). Detailed reviews describing the radiosensitization mechanisms triggered by AuNMs have recently published [70-72]; whereas, Cole et al. have discussed the nanomaterial optimized properties, such as composition, mass concentration, size, shape and surface functionalization, that ensure AuNM optimal functional performance as contrast agents in X-ray imaging and computed tomography [73].

In addition to radiosensitization, X-rays can be used as physical stimulus in conjunction with AuNMs to trigger specific therapeutic actions (e.g., drug release) or to allow for medical imaging by, for example, computed tomography (CT).

Stimuli-responsive AuNMs modifying their structure following an external physical trigger

Therapeutic applications

A schematic summary of the AuNMs described in this section is presented in Table 2.

Photo-responsive drug release

Light sources have been used in pre-clinical research to release therapeutic payloads (e.g., drugs, genes) from AuNMs employed as carriers [74]. This strategy offers the advantage to allow for the controlled release of the therapeutic active compound at a specific location and in a controlled manner. The

therapeutic dosage needed is therefore reduced and the side effects diminished, positively impacting on the treatment outcomes and safety [75]. An extensive literature review has been recently published on this topic [76].

The main mechanism by which photo-triggered drug delivery is achieved is the induction of AuNMs heating via the LSPR effect [77]. The photo-induced particle heating can be used to cause the thermal disruption of the non-covalent interactions between the payload molecules and AuNMs. Such structural changes are triggered via photo-caging or photo-isomerization [78]. These approaches have been used to affect the hydrophilic-hydrophobic balance of thermally responsive compounds coating the AuNMs surface (e.g., polymers or DNA [79-81]) or entrapped within the AuNMs, thus triggering the release of the therapeutic payload. For example, the LSPR photothermal effect was successfully used to release a chemotherapeutic drug (paclitaxel) loaded within poly(lactic acid-co-glycolic acid) (PLGA) microspheres that contained hollow gold nanospheres [82].

NIR light has been employed to induce the release of doxorubicin from hollow AuNMs via the LSPR photothermal effect [83, 84]. Also, gold nanospheres of 3–7 nm incorporated into the lipid bilayer of liposomes, have been used to fabricate photothermally responsive hybrid AuNMs capable of releasing fluorescein in a controlled manner [85]. Ma et al. incorporated gold nanoshells, doxorubicin, and magnetic nanoparticles into micelles made from cholesteryl succinyl silane. Upon laser irradiation, the photothermal heating of the gold nanoshells induced the micelles to collapse and resulted in doxorubicin release [63]. This photothermal approach can be used to induce deformation and rupture of gold nanoshells, where the therapeutic payload has been encapsulated, thus triggering its controlled release [84, 86-88]. A mechanism describing how drugs are released from these AuNMs when combined with laser-induced thermal therapy has also been proposed [89]. An alloy photo-responsive system formed by mesoporous silica-coated gold nanorods, was reported to be able to release doxorubicin in a stimuli-controlled manner [90]. Finally, a photo-responsive drug delivery system for the treatment of age-related macular degeneration, an ocular disease, was also developed based on polymer-coated AuNMs entrapped within an agarose hydrogel containing bevacizumab as therapeutic payload [91]. A localized temperature increase was induced by exposure to visible light, which caused hydrogel softening and subsequent drug release. These studies demonstrate that polymeric matrixes do not prevent light from reaching AuNMs and they do not compromise their photothermal properties. In parallel, photo-induced heating has been used to release oligonucleic acids from AuNMs via thermal dehybridization [92-96].

On the other hand, light irradiation can also induce payload release by mechanisms other than the LSPR photothermal effect, for example by disrupting the bonds that link the payload to the AuNMs surface. This drug delivery strategy is referred to as "light-triggered photocaged strategy," and it exploits NIR-sensitive covalent bonds or UV-aided, photo-cleavable molecular gates to link the therapeutic molecule to the AuNMs. For example, Sreejivungsa et al. developed AuNMs featuring light-responsive linkers capable of releasing a model drug (a naturally occurring compound extracted from *Goniothalamus elegans Ast*) following exposure to UV light [97]. Once irradiated with UV light, the linker was cleaved, leading to the release of the therapeutic agent. Agasti et al. used a photo-responsive o-nitrobenzyl linkage that upon UV light irradiation dissociated, for the controlled release of a caged anti-cancer drug (5-fluorouracil, 5-FU) from AuNMs [98].

Photo-responsive targeted therapy

Light can be used not only to induce payload release but also to determine the timing and specific location at which AuNMs will bind to the targeted tissue, to improve efficacy and decrease systemic toxicity. For example, Yeh and co-workers also established a smart photo-activated AuNMs drug delivery system that, upon UV light activation, can selectively target tumor cells and release an anti-cancer drug (Taxol) [99]. NIR irradiation has also been used to recover the function of surface-bound ligands blocked by steric hindrance on alloy (silica-gold) nanoshells [100]. YIGSR peptides were bound to the surface of the AuNMs but were prevented from binding their target by a coating of thermoresponsive pNIPAAm-co-pAAm copolymer. Upon NIR irradiation, the gold nanoshells heated up, causing the collapse

of the copolymer and exposure of the peptide, allowing cell targeting.

Photothermal therapy (PTT)

PTT is defined as the photon-mediated increase of localized temperature that can stimulate physiological responses. In anti-cancer therapy, PTT is used to kill cancer cells via the generation of localized heat between 43°C and 49°C [101].

As previously mentioned, when irradiated with a NIR laser source, AuNMs can convert the light into heat, allowing their use as PTT agents [102-106]. Pitsillides et al. reported the first demonstration of the use of AuNMs as PTT contrast agents [107]. The mechanisms by which AuNMs generate heat upon light irradiation through non-radiative processes are described elsewhere [108, 109].

Temperature distribution within the tumor tissue is critical to the efficacy of PTT. AuNMs photothermal conversion is directly proportional not only to the incident laser power and irradiation duration but also to the size and shape of the nanomaterial [38, 110-112], as discussed in detail in a recent review published on this topic [113]. Another recent review summarizes the heat-transfer and thermal-damage models that can be used to estimate the influence of these parameters on heat distribution in the tumor tissue [114]. Among the various AuNMs types, gold nanorods have been reported to be the best contrast agent for PTT [42]. However, their penetration in the tumor tissue can be limited, negatively impacting the heat distribution throughout the tumor and, ultimately, the success of the PTT treatment. Spherical AuNMs better accumulate within the tumor tissue. However, tumor retention of small AuNMs is challenging because they are rapidly cleared from the extracellular milieu. Additionally, spherical AuNMs need to be more than 50 nm in size to effectively absorb in the NIR region. To overcome this size limitation, spherical AuNMs decorated with photolabile diazirine moieties, have been developed as PTT agents [115]. When exposed to UV irradiation, the diazirine moieties caused the AuNMs to aggregate in the tumor site, changing their size and resulting in a significant shift in their LSPR peak towards the NIR region, which in consequence induced plasmonic coupling between adjacent AuNMs and remarkably enhanced their efficacy for PTT.

Photodynamic therapy (PDT)

PDT is another form of cancer treatment that utilizes light. Unlike PTT, which is oxygen-independent, PDT is completely dependent on the availability of oxygen in the tissue. In this technique, a photosensitizing agent (injected in the tissue) is excited at specific wavelengths, leading to the energy transfer, generation of ROS and cell death by apoptosis. AuNMs can act as photosensitizer agents. For example, Vijayaraghavan et al. developed lipid-coated gold nanoechinus (i.e., nanospheres with many spiky nanorods sticking out from the surface) that were capable of sensitizing tissues via singlet oxygen production for PDT applications [116].

Nevertheless, AuNMs have mainly been used as carriers to deliver photosensitizers to the target tissue [117, 118], thus overcoming the insolubility issue associated with the use of these compounds in physiological fluids. Gold nanostars have been used, for example, to deliver chlorin e-6, a PDT agent, allowing them to perform dual PDT/PTT therapy [119]. Other PDT/PTT dual therapies were developed by incorporating the photosensitizer hypocrellin into lipid vesicles containing gold nanocages [120], linking chlorin e6 to gold nanorods [121], or conjugating the photosensitizer indocyanine green onto gold nanospheres [122, 123]. Among stimuli-responsive AuNMs modifying their structure following light irradiation with application of PDT agents, we find gold nanorods conjugated to the photosensitizer AlPcS4 via electrostatic immobilization [124]. In this system, photothermal heating causes the release of the bound photosensitizer from the gold nanorod surface, allowing it to exert its PDT function.

High-intensity focused ultrasound therapy (HIFU)

When ultrasound is applied, the target tissue absorbs acoustic energy, triggering both thermal and non-thermal effects. In the thermal effects, tissue damage occurs as a function of the thermal increase. This is generally referred to as “sonodynamic therapy.” Because of the thermal effects, the cell membrane permeability

can also change, triggering endocytosis and enhancing the accumulation of the therapeutic within the cell. This process is called "sonoporation." The use of AuNMs in sonoporation has been explored in pre-clinical research for enhanced drug delivery applications [125]. On the other hand, non-thermal effects include cavitation, such as the formation of microbubbles within the tissue; these interact with the ultrasound field, which induced them to oscillate, grow and eventually implode (a process called "inertial cavitation" or "transient cavitation"). The microbubble collapse is associated with a shock wave, shear stress, high temperatures and ROS formation that can mechanically and chemically damage the cancer tissue. The acoustic fluence required to produce cavitation is very high. HIFU [126-128], a therapeutic technique that uses a US intensity that is several orders of magnitude greater than that of standard US, is used to achieve the required acoustic fluence. However, internal cavitation is difficult to control. To overcome such limitation, researchers have been using AuNMs as agents to lower the threshold of cavitation intensity, acting both as cavitation nuclei and promoting the collapse of the microbubbles [49, 51, 129-135]. Also, AuNMs aggregation, which induces thermal field overlap and plasmonic coupling, has been investigated as a method to further lower the required fluence levels [136].

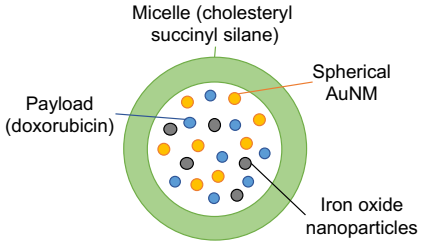
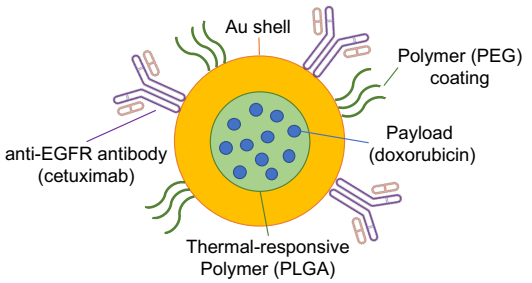
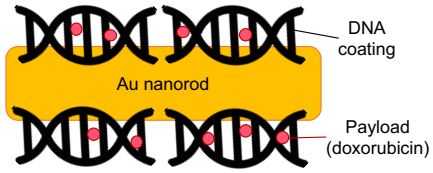
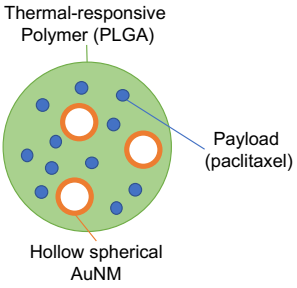
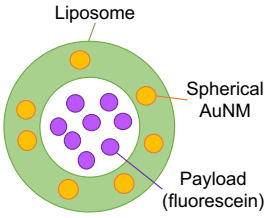
Focusing on physically triggered AuNMs or hybrid/alloy AuNMs whose structure is modified by the stimulus, PEGylated mesoporous silica nanocapsules, loaded with pyrene and perfluorohexane and functionalized on the surface with AuNMs, were formed [137]. In this alloy system, the AuNMs enabled for HIFU enhancement, which ultimately lead to the nanocapsule disruption and drug delivery, as demonstrated both in vitro and in vivo. Similarly, successful payload release was achieved from gold nanocages coated with the thermally responsive poly(NIPAAm-co-AAm) copolymer by exposure to HIFU [138]. In another study by Moon et al., gold nanocapsules were loaded with hydrophobic or hydrophilic drugs dissolved in a phase-change material (PCM) [139]. In this hybrid system, drug release is achieved when the PCM reaches the melting point, allowing the drug to diffuse out of the nanocapsules. HIFU was effective in controlling the drug release system by regulating the temperature and therefore the drug release profile.

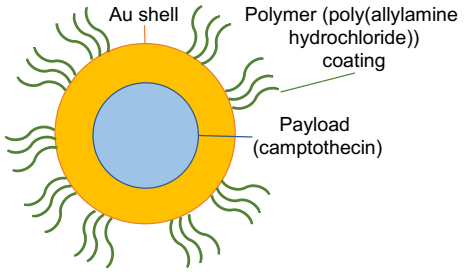
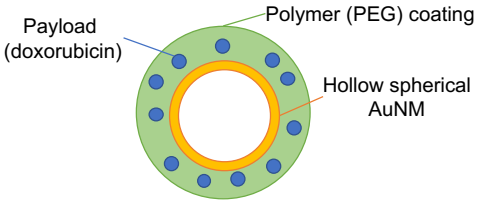
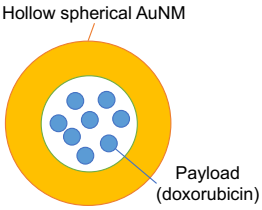
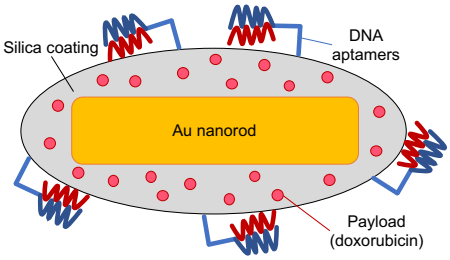
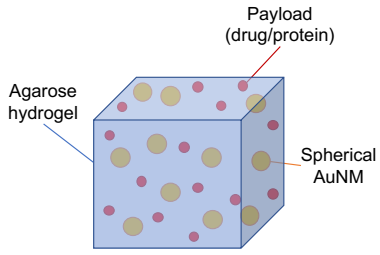
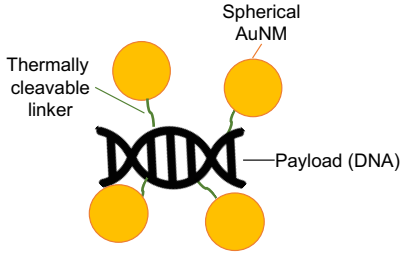
Radiotherapy

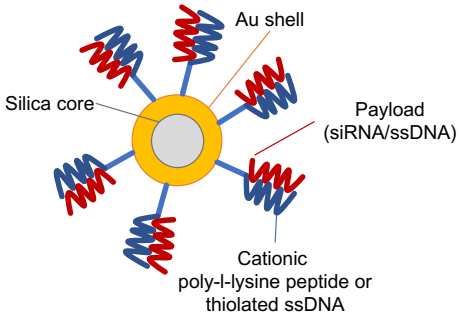
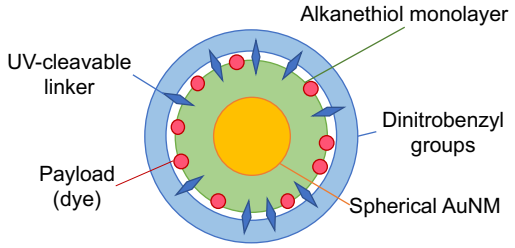
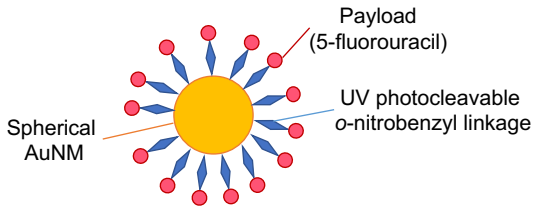
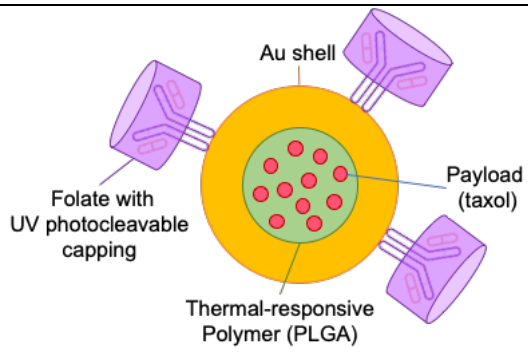
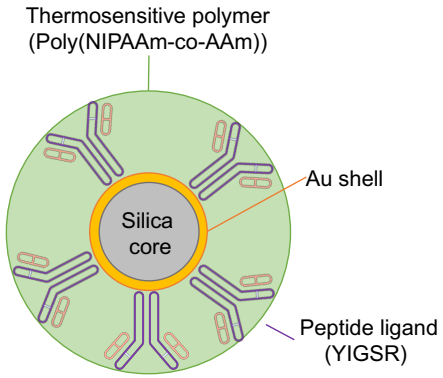
In radiotherapy, ionizing radiations (X-rays) are administered to tumor tissues to destroy the malignant cells directly or via the generation of free radicals. Owing to the strong X-ray absorption shown by AuNMs, the use of this nanomaterial in radiotherapy can lead to the enhancement of the local radiation dose while reducing other tissues getting radiated [70, 140-145]. Cui et al. demonstrated that the effect of radiosensitization by AuNMs is closely related to cellular uptake [146]. Similarly, AuNMs size has been demonstrated to play a key role in their ionizing properties: AuNMs with a size around 13 nm possess, for example, a superior radioactive disruption capability as compared to nanoparticles of other sizes [147]. Other than size, different AuNMs shapes also play an influence on their efficiency in radiotherapy, with spherical nanoparticles being the best ionizing agent to use [148]. Finally, various imaging modalities (e.g., PTT) and other therapeutic approaches can be coupled to radiotherapy when using AuNMs, to improve the therapeutic outcome [149-152].

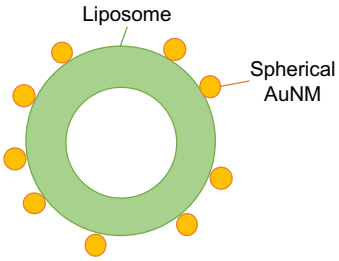
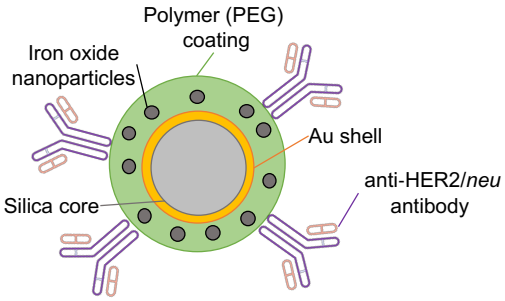
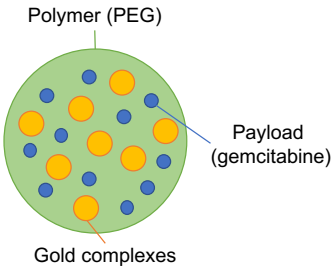
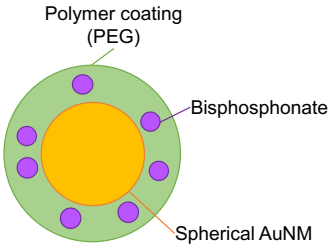
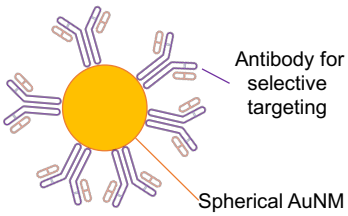
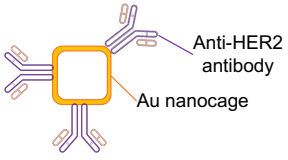
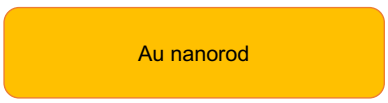
The AuNMs capability to amplify the X-ray local intensity can be used to develop smart drug delivery systems for selective drug activation [153]. Liu et al., for example, developed an X-ray-triggered nitrite release from nitroimidazole-functionalized AuNMs. Nitroimidazole is a pro-drug that, upon irradiation with X-rays, releases nitrite, a precursor of ROS, inducing the therapeutic effect against cancer cells [154]. The AuNMs radiosensitizing effect has also been exploited to trigger the release of an anti-cancer drug (doxorubicin, DOX) from DOX-conjugated DNA-coated AuNMs, resulting in a greater clonogenic cell kill compared to DOX-free DNA-coated AuNMs [155].

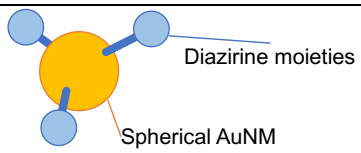
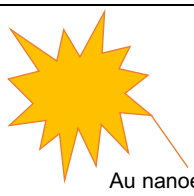
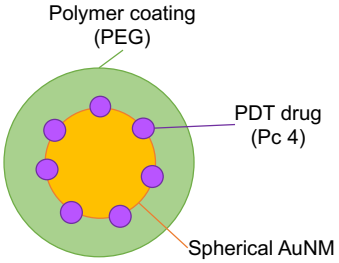
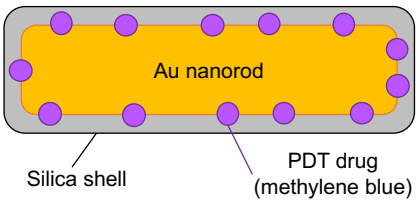
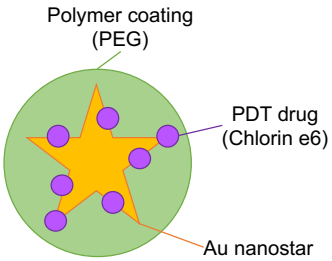
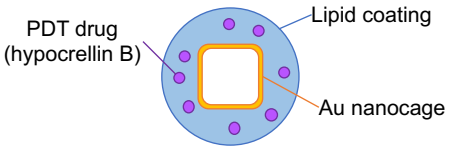
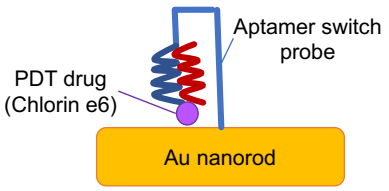
Table 2. Summary of the physically triggered AuNMs described in this review, for which the exogeneous stimulus applied induces a structural transformation or modification that is essential for their therapeutic action. The AuNMs and their chemical components are not drawn to scale.

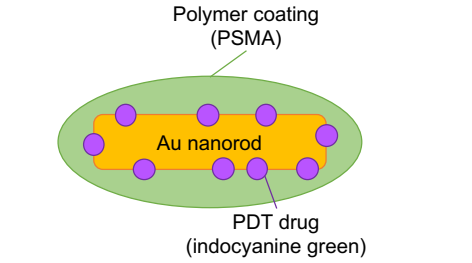
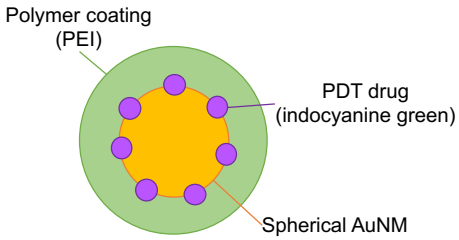
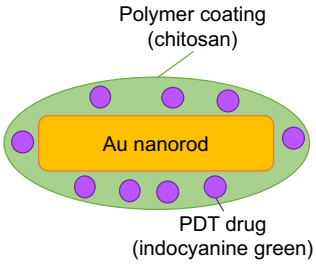
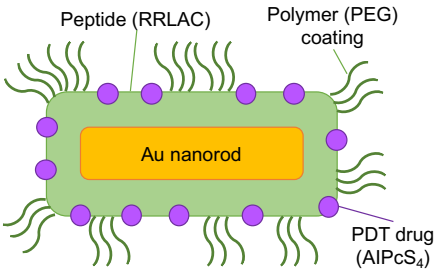
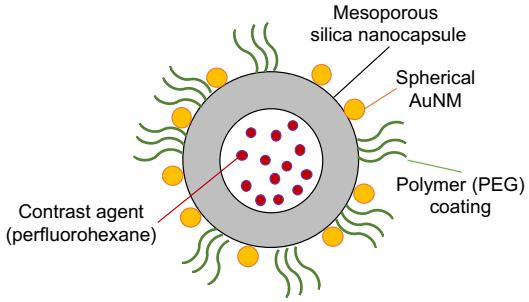
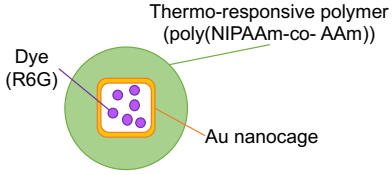
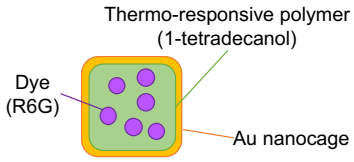
Therapeutic applications				
Physical stimulus type	Application	Strategy	AuNM structure	Ref
Laser light	Photo-responsive drug release	Thermal disruption of the compound coating the AuNMs surface or entrapped within the AuNMs, triggers the release of the therapeutic payload.		[63]
				[79]
				[80]
				[82]
				[85]

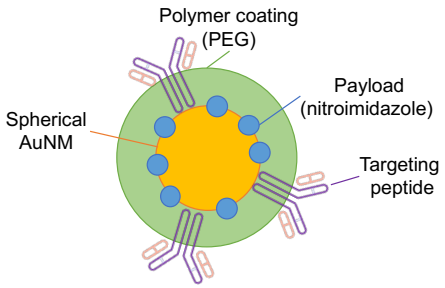
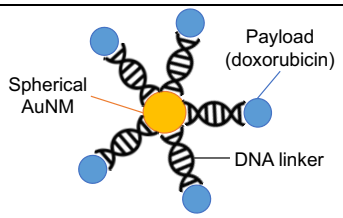
				[86]
				[83,84, 87]
				[89]
				[90]
				[91]
				[81]

		Thermal dehybridization allows the therapeutic payload (single-strand DNA, ssDNA, or siRNA) to be released.		[92-96]
		Photo-induced cleavage of the linkers conjugating AuNMs to the therapeutic payload.		[97]
				[98]
	Photo-responsive targeted therapy	Thermoresponsive polymers are used to mask a peptide ligand to control and reduce off-target effects.		[99]
				[100]

	PTT	Light absorption and conversion into heat trigger cell death.		[105]
				[106]
				[103]
				[104]
				[107]
				[112]
				[42]

				[115]
	PDT	AuNMs are used as photosensitizing agents.		[116]
		AuNMs are used as carriers to deliver photosensitizers.		[117]
				[118]
				[119]
				[120]
				[121]

			 	[122]
				[123]
				[124]
Ultrasound waves	High-intensity focused ultrasound therapy (HIFU)	AuNMs are used as HIFU agents, acting both as cavitation nuclei and promoting the collapse of the microbubbles within biological tissues.		[137]
				[138]
				[139]

X-rays	Radiotherapy	AuNMs release a payload upon stimulation with X-rays.		[154]
				[155]

Diagnostic applications

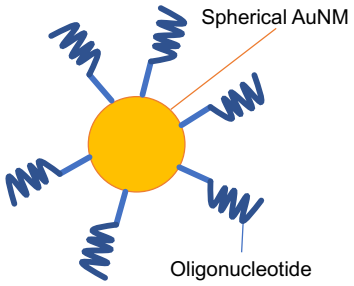
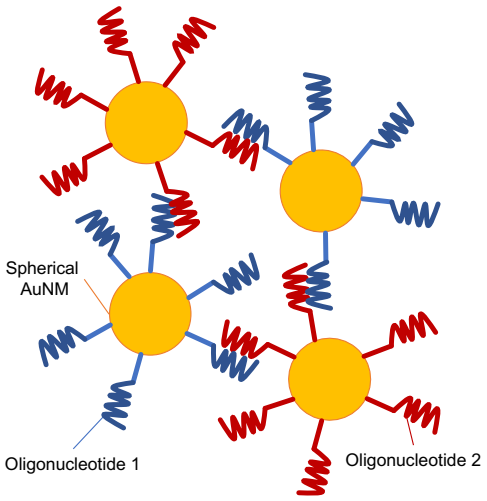
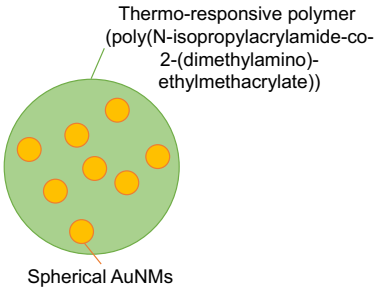
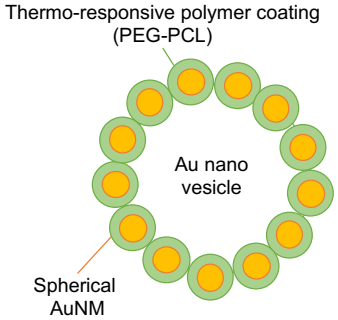
AuNMs activated by ionizing and non-ionizing external physical stimuli can generate various signals, including light, Raman or Rayleigh scattering and ultrasonic waves, that are useful for diagnostic purposes. Additionally, owing to their tuneable surface functionalities and light absorption/scattering, and enhanced extinction coefficient as compared to most common dyes, AuNMs ensure both the selective targeting of the analyte/tissue of interest and a strong detecting signal. Wilhem et al. recently reviewed the state of the art in this field [156]. To the best of the authors' knowledge, however, AuNMs modifying their structure upon external physical stimuli to exert their diagnostic function, are less frequent than those designed for therapeutic applications. To date, AuNMs belonging to this specific category have been used in diagnostics only as optical biosensors and photoacoustic imaging (PAI) contrast agents. These AuNMs are described in more detail below and a schematic summary is presented in Table 3. The use of this type of AuNMs as a contrast agent for dark-field microscopy (iDFM), Raman imaging, photoacoustic tomography (PAT), MRI, and CT, are also interesting applications in the diagnostic field, but are still to be explored by scientists.

Optical biosensors

A typical AuNMs-based biosensor monitors the frequency shift in LSPR resonance [157]. Thus, the simplest implementation of LSPR sensing is the use of AuNMs as a functional component of colorimetric assays both in liquid (homophase methods) and solid (dot immunoassay and immunochromatography) phase [1]. In these assays, AuNMs are conjugated with a bioactive moiety capable of binding with high-affinity specific analytes present in a solution [157, 158], such as biomolecules (e.g., proteins[159] or toxins[160]), small molecules (oligonucleotides [161]), ions (e.g., selenium [162]), or diseased cells (e.g., acute leukemia cells [163]). AuNMs-based optical sensors can also be used to detect specific antigens within the cellular compartments [164, 165]. In the presence of the analyte, the AuNMs-containing solution changes its optical/plasmon absorption (i.e., its color). These changes in the absorption spectrum can be easily detected either visually or spectrophotometrically, reaching a much lower limit of detection than conventional dyes. For example, conjugates of AuNMs-oligonucleotides are of great interest in the detection of DNA hybridization in the diagnosis of pathogenic and genetic diseases without the need of special instrumentation [1].

Thermoresponsive AuNMs are particularly useful in developing optical multiple aptasensors, such as DNA-aptamer-based colorimetric assays that can detect several targets at the same time in the liquid phase. In this instance, more than one class of aptamer (i.e., single-strain DNAs and oligopeptides with high binding affinity and selectivity for target molecules) are used to functionalize the surface of the AuNMs. The detection approach is based on the likelihood that the target DNA molecules

Table 3. Summary of the physically triggered gold nanomaterials described in this review, for which the exogeneous stimulus applied induces a structural transformation or modification that is essential for their diagnostic action. The AuNMs and their chemical components are not drawn to scale.

Diagnostic applications				
Stimulus type	Application	Strategy	AuNMs structure	Ref
Temper-ature	Optical multiplex biosensors	Target DNA molecules with different melting temperatures can be distinguished within the assay by AuNMs disassociation based on temperature.		[166, 167]
				[168]
		Thermoresponsive AuNMs are used as components of colorimetric assays to detect several targets at the same time.		[169]
Laser light	Photoacoustic imaging (PAI)	AuNMs act as a contrast agent.		[175]

have different melting temperatures, and therefore they can be distinguished within the assay by AuNMs disassociation based on temperature[166-168].

Similarly, a thermoresponsive AuNMs biosensor capable of distinguishing between homocysteine and cysteine has been reported [169]. The assay used AuNMs conjugated with thermoresponsive copolymers. Such conjugation induced the assembly of the AuNMs in a liquid phase, changing the solution color from red to bluish purple. Heating the solution induced AuNMs disassembly in the presence of cysteine, but not in the presence of homocysteine, which inhibited the process.

Photoacoustic imaging (PAI)

PAI is based on the sample irradiation with a laser, by which the energy of light absorbed by AuNMs, used as exogenous contrast agents [170-172], leads to the generation of waves in an ultrasonic range that are then converted into an image. Compared to MRI and CT, PAI offers various advantages including the use of non-ionizing irradiation, good spatial (5 μm-1 mm) and temporal (s-min) resolution, and improved sensitivity [173]. For example, AuNMs have been injected on-site into the tumor tissue, where they specifically bound to the cancer cells, helping to identify the malignant tissue and guiding the surgeons for precision treatment [174]. In PAI, larger AuNMs are preferred because of their higher scattering efficiency. Thus, multimodal gold nanovesicle, formed by the clustering of polymer-coated AuNMs, have been developed for simultaneous PAI and PTT [175]. Such clustering induces a shift in the absorption of AuNMs towards the NIR spectral region and a subsequent increase in PAI signal and image contrast, thus allowing to easily distinguish the tumor mass within the organ. Irradiation causes declustering of the gold nanovescicles, and the single AuNM components can be easily cleared from the body, avoiding systemic side effects.

Conclusions

In the last few decades, the growing incidence of chronic diseases associated with the increasing population aging, has triggered the need for more effective and localized therapies as well as efficient diagnostic tools for early disease detection [156]. AuNMs and alloy/hybrid AuNMs have been widely investigated to address this need. In this context, various synthetic strategies have been used to produce gold nanomedicines that enable target-specific treatments and robust diagnostic agents. The gold nanomaterials reviewed herein constitute the next-generation technology: they are AuNMs or hybrid/alloy AuNMs that are activated by external physical stimuli, where the therapeutic and/or diagnostic action is a result of the structural modification of the nanomaterial itself. Although this technology offers many advantages, such as a complete temporal and spatial control over the mode of action, these gold-based platforms are still at their infancy and they have not yet reached clinical phases. To increase the translation rate of this promising technology, the authors believe that future research efforts should focus on meeting clinical attributes, as recently discussed by Richardson et al. [176]. Such attributes should be investigated at the pre-clinical stages, to prove the existence of an advantageous risk-benefit ratio for patients. The adoption of the MIRIBEL (Minimum Information Reporting in Bio–Nano Experimental Literature) guidelines for published accounts of bio-nano research can support this activity [177]. On the other hand, technological requirements should also be satisfied, as pointed out over the years by experts in the field through many recent papers and reviews [178, 179], to ensure reproducibility and comparability [180]. We believe, within this frameset, an acceleration on the physically triggered gold nanomaterial products to clinics is foreseeable, with great achievements for the quality of life of patients.

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Conflict of Interests

The authors declare no conflicts of interest. For signed statements, please contact the journal office: editor@precisionnanomedicine.com

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