EXPERT OPINION

Gold nanoparticles in theranostic oncology: current state-of-the-art

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Introduction: In recent years, extensive multidisciplinary investigations have been carried out in the area of cancer nanotechnology. Gold nanoparticles (GNPs) have emerged as promising carrier for delivery of various pay-loads into their target. In view of their unique physicochemical and optical properties, GNPs have been exploited for multimodality imaging, tumor targeting, and as transporter of various therapeutics. Additionally, GNPs have been used as photothermal therapeutics against cancer.

Areas covered: This review will focus on recent progress in the field of gold nanomaterials in cancer therapy and diagnosis. Moreover, concern about the toxicity of gold nanomaterials is addressed.

Expert opinion: GNPs present versatile scaffolds for efficient delivery of cancer chemotherapeutics. Tuneable chemistry of the GNPs contributes to their ever increasing use in oncology research. The promises of a functional cancer therapy using GNPs have been extensively demonstrated, although the materials are still in their infancy stage and not surfaced to meet clinical standards.

Keywords: cancer therapeutics, gold nanomaterial safety, gold nanoparticle, nanocages, nano-oncology, nanorods, nanoshells, photothermal therapy

Expert Opin. Drug Deliv. (2012) 9(10):1225-1243

1. Introduction

The use of different nanotechnology-based drug targeting approaches to enhance the efficacy and to reduce side effects of anticancer drugs has been well established [1-6]. Engineered nanometric scale materials have unique properties which can improve the level of efficiency, reduced dosing frequency and/or lower toxicity in the treatment of cancer [4,7,8]. Nano-oncology is a new arena of interdisciplinary research involving biology, chemistry, pharmaceutical engineering and medicine aiming to achieve major advances in cancer diagnosis and treatment [3,9,10]. Literature forecasted that nanometric drug delivery carriers and bio-active nanomaterials are growing by more than 17% annually and will reach an estimated $18 billion market in 2014 [2]. Extensive research has been carried out to develop smartly designed nanoparticles (NPs) for therapeutics and diagnostics in oncology [2-14]. NPs formulations such as Doxil™, Abraxane™ (for therapeutic application) Resovist®, and Feridex® (magnetic NP based imaging agents of Liver tumors) have already surfaced and in clinical practice exemplifying the significance of targeted nanomedicines [14]. In case of Doxil™, development of bioequivalent generic version is already underway.

NPs used have unique features that distinguish them from conventional cancer therapeutics. First, NPs can have therapeutic or diagnostic properties by themselves. Second NP can be used as carriers for other therapeutically active agents, as they can be "piggybanked" with a therapeutic payload. Third, NPs can be surface functionalized with multivalent targeting ligands which yield high affinity and specificity for target cells. Fourth, NPs can accommodate therapeutics and imaging

informa healthcare

10.1517/17425247.2012.716824 © 2012 Informa UK, Ltd. ISSN 1742-5247

Article highlights.

- Gold nanoparticles (GNPs) have gained much attention as platform for drug delivery and diagnostic applications because of their unique surface characteristics, allowing easy functionalization with chemicals that alter their circulation behavior or redirect them to target cells.
- GNPs have been used as drug carrier by attachment of drugs to their surface.
- Changing the GNPs shape to nanorods, nanocages or nanoshells shift the absorption to the near infra red (NIR) region (650 – 900 nm), which is allows their use as nano-heaters in photo-thermal therapy.
- GNPs showed low toxicity compared to the other class of metallic nanoparticles.
- Gold nanomaterials can be applied as theranostic agents that can be used for both imaging and treatment of cancer.

This box summarizes key points contained in the article.

agents simultaneously, allowing combined chemotherapeutic and imaging strategies [8,12,13]. And finally, NPs may surpass drug resistance mechanisms as observed for classical agents used in oncology [2,3].

Till now, drug delivery research showcased a range of nanometric delivery vehicles such as dendrimers, liposomes, niosomes, nanoemulsions, carbon nanotubes, polymeric, and metallic NPs. Among the metallic NPs, gold nanoparticles (GNPs) have emerged as promising carrier for the delivery of various payloads into site specific targets [2,15-19]. Gold and gold-containing compounds have a long history of being used in medical practice [18,19]. Colloids of gold are still used in different system of indigenous medical treatment for renaissance, revitalization and rheumatoid arthritis [20].

GNPs are important biomedical tools in cancer research due to their unique light scattering nature and photothermal properties that do not require high-powered expensive lasers/microscopes to monitor the results [21-25]. Moreover, due to photothermal characteristics of GNPs, they can be used as cancer therapeutics. In recent years, GNPs have been explored with success to deliver variety of anticancer therapeutics along with their own theranostic applications [15]. **Figure 1** illustrates the multifunctional nature of GNPs and different bio-actives that can effectively deliver to the target tissue and cells. This review will enlighten the basic concepts and up-to-date research findings concerning the very promising use of gold nanomaterials in oncology. Particularly we address the recent progress in the functionalization of GNPs targeting tumor cells. Differently shaped GNPs exert different photothermal characteristics which has been exploited for the use of GNPs as the cytotoxic agents, as will be discussed. With the growing research to look for the possibility of different GNPs as cancer theranostic, their systemic toxicity needs to be thoroughly examined. With reference to the current update, we also address the safety aspects of intravenously administered gold nanomaterials.

2. Gold nanoparticles in nano-oncology

Gold nanomaterials have properties that make them particularly suitable for therapeutic applications in cancer [22-25]. In particular, Gold materials have unique optical properties with high absorption efficiency without the effect of photobleaching [25]. Due to enhanced surface area at the nano scale with gold nanomaterials, the light absorption and scattering efficiency may increase up to 4 to 5 times as compared to their macro counterpart. This feature makes them particularly attractive tools for cancer detection and therapy [25]. Moreover, gold nanomaterials in specific shapes like nano-rods, nano-stars, nano-cages and nano-shells show localized surface plasmon resonant properties that strongly favor their applicability in oncology. The plasmon resonance effect or surface plasmon resonance (SPR) is a state of resonant and collective oscillation of valence electrons in a solid when the electrons are irradiated by incident light. This manner of light absorption and emission of photon occurs with the same frequency in all directions. Once gold nanomaterials are adequately accumulated at the target site, they may cause irreversible localized thermal cellular destruction and imaging by the irradiation by the light of an appropriate wavelength due to SPR [26-28]. These features make GNPs excellent theranostic nanometric systems with prospective opportunity for therapeutic treatment cancer in deeper tissues.

3. Tumor targeting potential of surface functionalized gold nanoparticles

Many new drugs and biomolecules have been reported for the treatment of cancer. However, the clinical potential of such chemotherapeutic agents are subjected to certain physiological, therapeutic and toxicological limitations, such as the barrier effect of the cellular membrane, drug disposition behavior and drug resistance developed by the cancerous cells by means of elevated expression of drug transporters or drug metabolizing enzymes [29]. As seen in case of conventional chemotherapy, the majority of chemotherapeutic agents display a large volume of distribution and penetrate into healthy organs and tissues [30,31]. Drug targeting strategies, in contrast, constrain the distribution of drugs to specific organs and hence provide opportunities to reduce side effects and enhance efficacy. The inherent poor solubility of most of the (small molecule) anticancer agents in water and physiological fluid is another dilemma associated with chemotherapy which necessitates the use of pharmaceutical solvents for their administration. Such co-solvents may sometime have life-threatening effects due to their systemic toxicity [3,32]. Nanotechnology-based delivery approaches may overcome the solubility issues. Several investigators have illustrated the feasibility of GNPs in terms of easy in synthesis [33-42] and having potential to improve cancer therapy by preventing multidrug resistance and increasing the therapeutic index of anticancer drugs by prolonging drug systemic

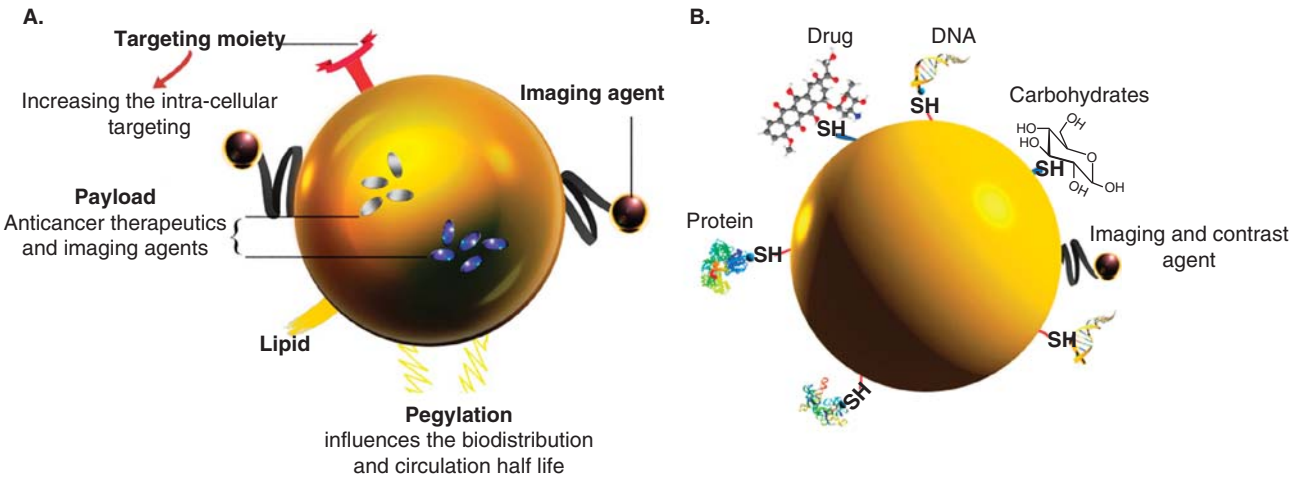

Figure 1. Diagram showing the Multifunctional nature of GNP; A) active targeting ligands like folic acid, antibodies or peptides can be conjugated to GNP. Surface modification with hydrophilic polymers like PEG can improve the passive targeting characteristics; **B)** Different class of bio-active molecules can be conjugated or incorporated with GNPs, in order to address their targeting to target tissues and cells.

circulation lifetime, targeted drug delivery, stimuli-responsive drug release, endocytic uptake of drugs and co-delivering chemo-sensitizing agents [22-25,43].

Commonly there are two strategies for therapeutics targeting in cancerous tissues; "passive targeting" which depends on the leaky vasculature of the diseased tissues that provide EPR effect to the carrier systems [44] and "active targeting" that involves the functionalization of therapeutic delivery carrier by the attachment of affinity molecules that interact with specific cell receptors (**Figure 2**) [45]. Similar strategic approaches were adopted in case of GNPs in oncology. Here we discuss the GNPs based cancer targeting prospective with reference to the recent investigations. The highly tunable and multivalent facade of GNPs offers opportunities to integrate multiple therapeutics by covalent or non-covalent conjugation [43,46,47].

Several types of targeting ligands have been used for active targeting of GNPs, of which we will discuss some highlights in this review. It was found that around 100 of ligands can be covalently conjugated to GNPs with a 2 nm core diameter [48]. As first example of active targeting, PEGylated GNPs were developed and conjugated with human transferrin (Tf) by amine-carboxylate reaction. First, Tf-equipped GNPs showed significantly improved uptake in cancer cells, as was demonstrated after i.v. administration to mice bearing Neuro2A tumors [49]. Of note, the biodistribution of GNPs was independent of the Tf content, but the subsequent uptake by targeted cells was improved. In another study, however, GNP organ distribution was influenced by the amount of Tf targeting ligand coupled to the NPs; it was found that GNPs were poorly up-taken up and thus small amounts of the NPs reside in hepatocytes of liver tissues [50]. Other examples of active targeting of GNPs were illustrated by the investigators. Over expression of folate receptors (FR) is a common feature of many tumors. FRs can effectively be targeted using folic acid (FA) and methotrexate (MTX) and its derivatives as ligands [51]. Dixit and coworkers recently used this principal and demonstrated the delivery of MTX by FA conjugated MTX-GNPs in folate receptor-positive KB cells [52]. In addition to a targeting moiety, MTX also serve as well known chemotherapeutic agent. Direct utility of MTX with dual function as MTX–GNPs was further demonstrated by Wu Shiau and coworkers in a mouse ascites model of Lewis lung carcinoma (LL2) [53]. Recently, similar research has been reported in which simultaneous conjugation of FA and DOX or FA and cisplatin have been carried [54,55]. Amphiphilic GNPs were assembled in the manner that hydrophobic poly L-aspartate-doxorubicin coupled in the inner hydrophobic shell by covalent conjugation with an acid-labile hydrazone linkage [54]. DOX- GNPs were reported with fast release behavior in acidic pH (pH-5-6). Such an approach is particularly advantageous for pH-triggered drug release to the slightly acidic environment of tumor tissues [55]. Moreover, Wang *et al.* designed a different type of DOX-GNPs in which DOX was conjugated to GNP with acid labile bond via poly ethylene glycol [56,57]. Chauhan *et al.* used a cellular extract of *Candida albicans* for biogenic synthesis of GNPs [58]. They demonstrated the potential of GNPs as probe in liver cancer cells by conjugating them with in-house produced polyclonal antibodies directed to liver cancer cells [58]. Recently, Unak *et al.* illustrated the radio-sensitization efficacy of gold nanomaterials against cancer cells. They designed a targeted GNP by attachment of anti-metadherin (Anti-MTDH), an antibody that binds to a receptor over expressed on breast cancer cells [59]. These NPs were furthermore labeled ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG), a tracer that can be monitored by positron emission tomography/computational

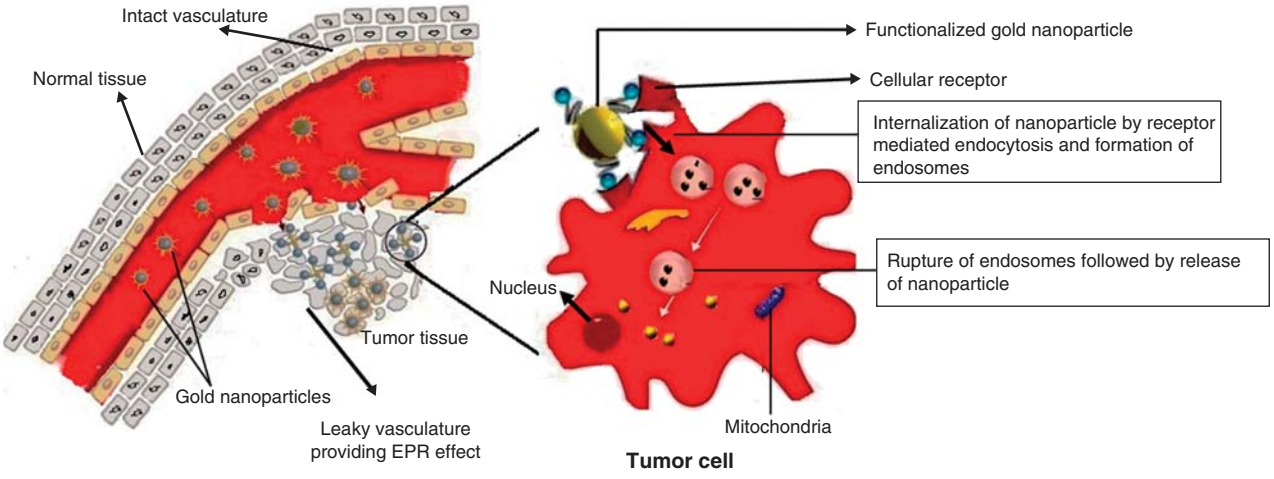

Figure 2. Schematic representation of passive targeting (due to enhanced permeability and retention effect (EPR) because of leaky vasculature in the tumoral tissues) and active drug targeting (based on interaction of GNPs with surface-exposed receptors on target cells, promoting internalization).

tomography (PET/CT), but also can serve as radiotherapeutic agent. It was found that Anti-MTDH-GNPs significantly improved the imaging and cell killing because of active cell targeting due to presence of Anti-MDTH. Likewise, the apoptotic cells ratio of MCF7 cells was increased from 2.0 to 20% on treatment with this complex nano-system as compared to non-treated MCF7 cell line [59].

Attachment of polyethylenglycol (PEG) to GNPS helps in increasing their passive targeting, as PEGylation reduces the interaction with cells and prolong the circulation time of the NPs. PEGylation of NPs is a commonly applied strategy that reduces the clearance of NPs by the reticolendothelial system, as was also demonstrated for GNPs [15]. Moreover, bifunctional PEGs are often used for the attachment of targeting ligands, thus combining the positive properties of PEG shielding with the targeted accumulation in target cells via the appended homing ligand. Peng *et al.* synthesized PEGYlated GNPS by entrapment of a PEGylated dendrimer within the NPs. They studied the imaging properties of these GNPS in a xenograft tumor model in mice [60]. Their findings suggest that the PEGylated dendrimer-entrapped GNP is long circulating and that it can be used as a promising contrast agent for computational tomography (CT) imaging of various biological systems in cancer diagnosis. Heo *et al.* synthesized PEGylated GNPs linked to beta-cyclodextrin (β-CD) which was subsequently loaded with either paclitaxel (PTX) or rhodamine B as a theranostic for cancer therapy [61]. This type of GNPs released PTX in control manner under the influence of intracellular glutathione level.

In addition to attachment of targeting ligands and PEGylation, the surface and core of GNPs can be functionalized by surface charge and decorated with drug payload. Recently, Gibson *et al.* developed GNPs (~ 2 nm and having narrow PDI) that were covalently conjugated with Paclitaxel [62]. Thermographic analysis of PTX-GNPs showed that the content of the covalently attached drug was nearly 67% by weight corresponding to 70:1 PTX to GNPs loading [62]. Efficient release of drugs from such covalently conjugated GNPs was reported by various methods including hydrolysis by phosphodiesterases [63]. Platinum(IV) based anticancer molecules were linked via oligonucleotides tp GNPs and used as pro-drug for tumor cells; these NPs released their cargo via intracellular reduction of pro-drug to the active Pt (II) form which resulted in cytotoxicity activity [64].

Kim *et al.* investigated the influence of surface charge on localisation of the GNPs in tumor cylindroids [65]. They showed that the rate of cellular uptake of positive and negative charged GNPs was fast in apoptotic and necrotic tissues. Interestingly, the uptake kinetics of positive charged GNPs was irreversible, while it is reversible for negative charged GNPs [65]. This finding suggested that positive charged GNPs may serve as the effective therapeutic carrier as they are more significantly accumulated in the proliferating cells [65]. In a similar study, intracellular glutathione-mediated release of doxorubicin from GNPs was examined in tumor cylindroids; this study showed the importance of a positively charged surface of GNPs in promoting permeation enhancement and drug accumulation in the cell [65]. Size dependent biodistribution and efficacy was also addressed in case of GNPs.

Aside from small drug molecules, GNPs have also been loaded with larger therapeutics such as bioactive proteins. An advanced example of such an approach is the nanomedicines CYT-6091, a PEGylated GNP decorated with the cytokine TNFα [66]. The main mechanism of action of this type of NPs is that the absorbed TNF is slowly released from the GNPs after their accumulation in the tumor. PEG-GNP-TNF prolonged the residence of TNFα in the

circulation and more importantly- provided elevated levels of TNFα that persist for several hours post administration [15]. CYT-6091 has been evaluated in Phase-I clinical trials, and demonstrated less systemic toxicity compared to the equimolar dose of neat TNFα [66]. More recently, even further enhanced anti-tumor efficacy was observed for GNPs grafted with thiolated paclitaxel onto cAu-PEG-TNF [16].

Irradiation of GNPs with near infra red (NIR) light generates heat, which can be employed for triggered drug release from heat-sensitive formulations. Such an approach has for instance been used to trigger drug release from hydrogels, but also more smart materials have been developed [67]. The generated heat may synergise the chemotherapeutic effect of drug that targeted to the cancerous site [67,68]. These theories were adopted in the development of GNPs coated with thermo-sensitive shell of poly (N-isopropylacrylamide) hydrogel (serve as the drug reservoir) [67]. For easy understanding of the reviewed subjects, GNPs and their multifunctionality as targeted therapeutic carrier and self theranostic are summarized in **Table 1**.

4. Photothermal effect of gold nanomaterials and their theranostic application

On irradiation of gold nanomaterial with near light in the infra red region, the excited electrons of different atomic levels and sub-levels come to ground state by emitting the energy in the form heat and raise the temperature to the surrounding. The temperature may rise depending on the shape and concentration of the gold material, power of the lesser, exposure time [69,70]. In physical terminology, this photothermal effect is termed as localized surface plasmon (LSP) resonance which is a charge density oscillations restricted to metallic nanostructures [70]. LSP occurs with specific frequency of light and depend on shape, size and surface of the particles that result in enhancement of electromagnetic fields along with strong light scattering and absorption [70]. GNPs can be used as locally accumulated energy transducers or nano-heaters, when they—subsequent to their injection and intratumoral accumulation—are irradiated by lasers. The absorbed energy is dissipated as heat and will kill adjacent cancer cells. This unique inherent characteristic of gold nanomaterial surfaced the application of GNP in different nanometric shapes for photothermal therapy, in addition to their use as drug carrying NPs. O'Neal and coworkers demonstrated for the first time the thermal ablation of tumors following exposure of tumors to localized gold particles to NIR light [27]. Huang *et al.* further reported on the potential use of this technique [71]. In their study, they coated the GNPs with anti- EGFR (epidermal growth factor receptor) as targeting ligand to get high accumulation in HSC3 tumors. It was found that anti-EGFR conjugated GNPs enhanced the efficacy of photothermal death of the cancerous cells by 14 and 20 times, as compared to the cellular distruction without anti-EGFR conjugated GNPs and GNPs respectively [71].

In another investigation El-Sayed *et al.* recorded the SPR scattering image and SPR absorption spectra from naked and anti-EGFR conjugated GNPs on incubation in non-malignant and malignant oral epithelial cell lines [72]. As expected, anti-EGFR- GNPs bound more specifically to the human oral squamous carcinoma cell lines with 600 fold greater affinity than to non-cancerous cells. Their results suggest that SPR scattering imaging generated from GNPs can be useful in molecular biosensors technique for the diagnosis of cancer and exploration of oral epithelial cancer cells *in vivo* [72]. Diagnostic characteristics of GNPs were explored to new dimension with the case study of liver cancer. Li *et al.* ascribed a unique strategy for simultaneous determination of multiple liver cancer biomarkers based on redox labels with distinct voltammetric peaks. GNPs coated carbon nanotubes were used as carrier and amplifier for immobilize redox probes labeled antibodies [73]. As a recent development in the prospective of GNPs theranostic, Geng *et al.* synthesized thioglucose bound gold nanoparticles (Glu-GNPs) that can be used as a sensitizer to enhance ovarian cancer radiotherapy [74]. They studied the effect of Glu-GNPs in human ovarian cancer cells (SKOV3) and compared the results to treatment of cells with irradiation alone [74]. An approximate 31% increment in NP uptake was observed in case of Glu-GNPs as compared to naked GNPs. This enhanced cellular accumulation of Glu-GNPs resulted in increased efficacy of irradiation induced cell killing, which was increased by 26.88% for 6 MV irradiation along with the Glu-GNPs, as compared to irradiation alone. The possible rationale behind the enhanced cell death is due to thioglucose mediated high accumulation of GNPs that interact with X-ray radiation and raised the level of ROS production that subsequently enhance the radiotherapy of ovarian cancer [74]. In recent time many reports were published in favor of photothermal characteristics of GNPs and their effect in different kinds of cancer [75-87].

Lukianova-Hleb *et al.* addressed the problem of non-selective uptake of GNPs, by developing a technique that is only effective when the uptake of GNPs has reached a certain threshold [88]. Different types of antibody-equipped GNPs were studied for selective targeting and activation in a heterogeneous *in vitro* biological microenvironment of prostate cancer and stromal cells. Although GNPs were accumulated to some extent in both cancer cells as well as non-cancerous stromal cells, the uptake was highest in cancer cells due to receptor mediated endocytosis via the antibody-target receptor recognition. When irradiated with laser energy of specific wavelengths but at low fluence, i.e., low energy intensities, cell-destructive plasmonic nanobubbles (PNBs) were only created in target cells that had accumulated larger amounts of the GNPs. As such, therapeutic selectivity of PNBs was achieved [76,88]. Van de Broek *et al.* reported the concurrent cell targeting and photothermal therapy with nano-body (VHH) conjugated branched GNPs [77]. Flow cytometric analysis and dark field images confirmed that these

Table 1. Examples of different Gold nanomaterials showing their multi-functionality as targeted therapeutic carrier and self theranostic in oncology.

Gold Nanomaterials	Surface functionalization/ drug loading	Targeting approaches	Tumor model/cell line	Remarks	Ref.
As drug carrier					
Gold nanoparticles (GNPs)	GNPs covalently functionalized with *Paclitaxel* via hexaethylene glycol linker	–	–	High drug loading at very low size (~ 2 nm) of carrier (approximately 70 molecules of paclitaxel per 1 GNP)	[62]
Gold nanoparticles (GNPs)	*Paclitaxel* conjugated to GNPs via phosphodiester moiety	Passive	–	paclitaxel is liberated in presence of phosphodiesterases	[63]
Gold nanoparticles (GNPs)	Oligonucleotide functionalized *Cisplatin* pro-drug (Pt(IV) GNPs	Passive	Human lung carcinoma A549, human prostate cancer PC3, cervical cancer HeLa, and human osteosarcoma U2OS cells	Pt(IV)conjugated via oligonucleotides to GNPS. (pt IV) GNPs can be served as single agent for combination therapies as DNA-GNPs are known to knockdown gene expression	[64]
Gold nanoparticles (GNPs)	*Methotrexate* (MTX)		Hepatocellular carcinoma cell lines (LL2 and ML-1) and bladder cancer cell line (MBT-2), human prostate cancer (PC-3) and human cervical cancer cell line (HeLa)	MTX-GNPs shows concentration dependent higher cytotoxic effects on tumor cell lines in comparion to free MTX	[53]
Gold nanoparticles (GNPs)	Thiolated PEG capped with *Oxaliplatin*	Passive	Lung epithelial and colon cancer cell lines	Improved cytotoxicity versus oxaliplatin alone in all of the cell lines; penetration of GNPs into the nucleus	[58]
Gold nanoparticles (GNPs)	*Cisplatin* and folic acid conjugated by PEG spacer	Active	Ovarian cancer cells (OVCAR-5 and OV-167 cells)	cisplatin-GNPs showed cytotoxic effects in tumor cells; no toxicity in normal cells	[55]
Gold nanoparticles (GNPs)	*Doxorubicin* conjugated by PEG spacer	Passive	Multidrug resistant MCF-7/ADR cancer cells	pH responsive release of doxorubicin in acidic organelles following endocytosis. Induced elevated apoptosis of MCF-7/ ADR cancer cells Excellent therapeutic potential and ability to probe drug release in *in-vivo*	[57]
Gold nanoparticles (Aurimune™; CYT-6091)	Recombinant human tumor necrosis factor alpha (rhTNFα) loaded onto PEGylated GNPs	Passive/Active	Human prostate tumor-bearing nude mice	PEGylated rhTNFα loaded GNPs facilated the selective uptake of TNFα by the tumor tissue and there was an absence of side effects either from TNF and GNPs	[134]
			Phase-I clinical trial in Advance stage solid tumor bearing subjects	Aurimune™ was well tolerated at doses of 50 μg/m^2 to 600 μg/m^2. It effectively targeted to tumors in human subjects	[66]
Gold nanoparticles (GNPs) PT-cAu-TNF	Thiol-derivatized PEG (PT) conjugation and loading with recombinant human TNF		MC-38 colon carcinoma tumors grown in mice	On i.v administration, PT-cAu-TNF preferentially accumulated in MC-38 colon carcinoma tumors and showed little or no accumulation in healthy organs	[135]

Table 1. Examples of different Gold nanomaterials showing their multi-functionality as targeted therapeutic carrier and self theranostic in oncology (continued).

Gold Nanomaterials	Surface functionalization/ drug loading	Targeting approaches	Tumor model/cell line	Remarks	Ref.
As theranostic agent					
Gold nanoparticles (GNPs)	PEG-folate-coated GNPs	Active	FR^+KB cells (human cancer cell line of nasopharyngeal origin) with over express folate receptors	Sterically stabilized nanoparticles exhibited selective targeting to KB cells	[52]
Gold nanoparticles (GNPs)	GNPs Conjugated with liver cell specific LCCS antibody	Active	liver cancer cells carrying female BALB/c mice	Unique biogenic mode of GNP synthesis With antibody-conjugation, GNPs successfully differentiated cancer cells from normal cell populations	[58]
Gold nanoparticles (GNPs)	GNPs Conjugated with anti-metadherin (anti- MTDH) antibody and [^{18}F]2-fluoro-2-deoxy-d-glucose (^{18}F-FDG)	Active	MCF7 breast cancer cell line	Radiosensitization by anti-MTDH-GNPs improved the radiotherapy (as apoptotic cell ratio increased from 2 to 20%)	[59]
Gold nanoparticles (GNPs)	PEGylated dendrimer-entrapped in GNPs	Passive	Xenograft tumor model in nude mice	Promising contrast agent with enhanced biocompatibility for CT imaging in cancer diagnosis	[60]
Gold nanoparticles (GNPs)	PEGylation and surface coating with human transferrin (T_f)	Active	Mice bearing Neuro2A cells	PEGylation allowed steric stability against salt- and serum-induced aggregation. Active targeting showed Tf-dependent internalization	[49]
Gold nanoparticles (GNPs)	Conjugated to monoclonal anti-epidermal growth factor receptor (anti-EGFR) antibodies	Active	Malignant oral epithelial cell lines (HOC 313 clone 8 and HSC 3)	Improved *in-vivo* biosensor due to cell specific targeting and enhanced SPR scattering and absorption	[72]
Gold nanoparticles (GNPs)	*Paclitaxel* loaded GNPs surface-functionalized with PEG, biotin, (PTX) and rhodamine B	Active	HeLa, A549 and MG63	Served as excellent cancer targeted theranostic agent due to presence of anticancer *Paclitaxel* and fluorescent probe rhodamine B	[61]
Gold nanorods (GNRs)	PEGylated GNRs	Passive	Human glioblastoma (U87)	Thermal response of GNPs allowed temperature controlled release of doxorubicin from thermosensitive liposomes	[73]
Gold nanorods (GNRs)	PEGylated GNRs	Passive	Wistar rat	Long circulating GNRs demonstrated reversible, pulsatile phase transition and localized killing of cancerous cells in kidney region using NIR laser	[67]
Gold nanorods (GNRs)	Conjugated to monoclonal anti-epidermal growth factor receptor (anti-EGFR) antibodies	Active	Human oral cancer cells (squamous cell carcinoma)	Anti-EGFR GNRs selectively accumulated in cancer cells. High surface plasmon field due to strongly enhanced Raman scattering by aligned nanorod arrays	[80]

Table 1. Examples of different Gold nanomaterials showing their multi-functionality as targeted therapeutic carrier and self theranostic in oncology (continued).

Gold Nanomaterials	Surface functionalization/ drug loading	Targeting approaches	Tumor model/cell line	Remarks	Ref.
Gold nanorods (GNRs)	Conjugated to monoclonal anti-epidermal growth factor receptor (anti-EGFR) antibodies	Active	Malignant oral epithelial cell lines (HOC 313 clone 8 and HSC 3)	Strongly scattered red light from GNRs in targeted cells lead to efficient cancer cell diagnostics and selective photothermal therapy	[114]
Gold nanorods (GNRs)	Functionalized with folate	Active	KB cells	Functionalized nanorods accumulated on the cell surface and rendered the tumor cells highly susceptible to photothermal damage	[117]
Gold nanorods (GNRs)	PEGylated Nanorods	Passive	squamous cell carcinoma xenografts in mice	Plasmonic photothermal therapy (PPTT) over a 13-day period, with resorption of > 57% of the directly-injected tumors and 25% of the intravenously-treated tumors	[118]
Gold nanorods (GNRs)	PEGylated Nanorods	Passive	Mice bearing orthotopic ovarian tumors	longer circulation time in the blood and higher accumulation in the tumors	[127]
Gold nanorods (GNRs)	Surface functionalized with cyclic RGDfK peptide	Active	DU145 prostate cancer	RGDfK surface-modified GNRs showed selective binding and uptake by endothelial cells	[120]
Gold nanorods (GNRs)	Chitosan-conjugated pluronic-based GNRs	Passive	Squamous cell carcinoma (SCC7) and NIH/3T3 fibroblast cell line	long circulation time, a good tumor accumulation, low liver uptake and enhanced photothermal ablation of cells	[129]
Gold nanorods (GNRs)	Surface functionalized with A33scFv	Active	Antigen-expressing SW 1222 cells (colorectal carcinoma)	Photothermal therapy with targeted A33scFv-GNRs showed significantly greater cell death	[122]
Gold nanorods (GNRs)	GNRs conjugated to three different ligands: (i) single-chain variable fragment (ScFv) peptide targeting EGFR (ii) amino terminal fragment (ATF) peptide targeting urokinase plasminogen activator receptor (Upar); and (iii) a cyclic RGD peptide that recognizes the $\alpha_v\beta_3$ integrin receptor	Active	Xenograft tumor models	GNRs functionalized different targeting ligands. After i.v. administration, tumor accumulation is mainly driven by passive targeting (no difference with PEGylated GNRs) Stiking differences in cellular distribution of GNRs, depending on type of targeting ligand	[136]
Branched GNPs	Conjugated with anti-HER2 nanobodies	Active	HER2 positive SKOV3 cells	Effective antigen-targeted photothermal therapeutic agents for cancer treatment	[77]
Gold nano-stars	Coated with a silica shell containing methylene blue (serves as photosensitizing drug for singlet-oxygen generation)	Passive	BT549 breast cancer cells	Combination of SERS detection (diagnostic) and singlet-oxygen generation (therapeutic) made the system a excellent theranostic	[109]

Table 1. Examples of different Gold nanomaterials showing their multi-functionality as targeted therapeutic carrier and self theranostic in oncology (continued).

Gold Nanomaterials	Surface functionalization/ drug loading	Targeting approaches	Tumor model/cell line	Remarks	Ref.
Gold nanoparticles (GNPs)	covalent coupling of gold nanoparticles to retargeted adenoviral vectors	Active	Colon adenocarcinoma cells (MC38 CEA-2 cells)	A new approach in which GNPS are attached to adenoviral vectors. The viral vector serves as targeting ligand and allows combination therapy of hyperthermia and gene therapy	[137]
Gold nanocages (GNCs)	Conjugated with anti-HER2 antibodies	Active	Breast Cancer (MCF7)	Specific targeting to breast cancer cells and serve as excellent contrast agents for optical imaging	[84]
Gold nanocages (GNCs)	Conjugated with monoclonal antibodies (anti-HER2)	Active	Breast Cancer (MCF7)	Strongly absorbed light in the NIR region with an intensity threshold of 1.5 W/cm^2 to induce thermal destruction of cancer cells	[87]
Gold nanoshells (GNSs)	GNSs with Superparamagnetic iron oxide (SPIO) core	Passive	Breast cancer cells (MCF7)	Cellular targeting was controlled by an external magnetic field. Enhanced efficacy of photothermal therapy by GNSs	[82]
Gold nanoshells (GNSs)	Functionalized with a A54 peptide against liver cancer cells	Active	Liver cancer cells	Target cell-selective photothermal killing. Imaging of hepato-carcinoma	[106]
Gold nanoshells (GNSs)	GNSs composed of a superparamagnetic iron oxide (SPIO) core	Passive	A431 tumor cells	Efficient photothermal ablation of cancer cells under MRI guidance, as well as the ability to target solid tumors under an external magnetic field	[113]

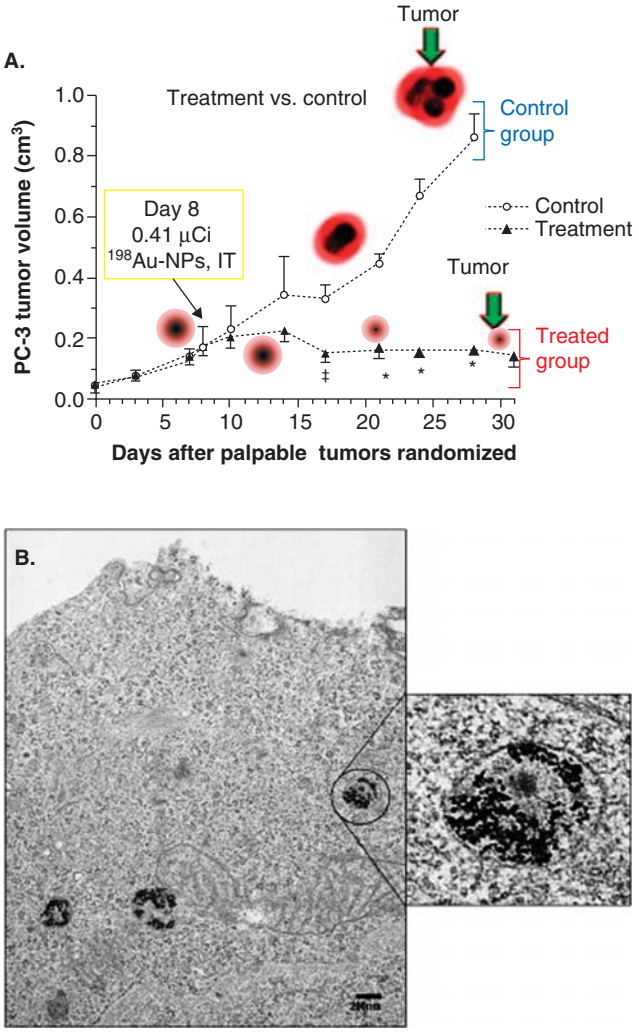

Figure 3. Effective tumor therapy using Gum arabic glycoprotein (GA)–functionalized gold nanoparticles (GA-GNPs). A. Therapeutic efficacy of GA-GNPs in prostate tumor bearing SCID mice after a single intratumoral injection. **B.** TEM imaging showing the uptake of GA-GNPs in prostate cancer.

**P = 0.005; day 17

*P < 0.0001; days 17-28 n = 5-7; means ± SEM

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VHH conjugated branched GNPs specifically bind to the HER2 positive SKOV3 cells [77]. Targeted tumor cells were easily destroyed just after the 5 min of laser irradiation [77]. Kannan *et al.* [78] and Chanda *et al.* [79] independently investigated the effect of β-emitting radioactive GNPs for cancer targeting in prostate tumors.

Chanda *et al.* evaluated the cancer targeted therapeutic prospective of beta-emitting ^{198}Au-GNPs that had been coated with Arabic gum glycoprotein. *In vivo* investigation (illustrated here in **Figure 3**) demonstrated high efficacy (82% tumor reduction) of an intratumoral single dose of GA-^{198}Au-GNPs in immune-deficient mice model inoculated with human prostate tumor xenografts [79]. In a similar kind of investigation, Kannan *et al.* reported findings corroborating the above results [78]. So, GA-^{198}Au-GNPs may serve as an effective approach for prostate tumor targeting that allows ablation of the tumor with minimal or no affect the normal cells. Literature confirmed that scattering and absorption in the NIR region that leads to the generation of the thermal effect predominantly dependent on shape of the nano metric gold material rather than the size [80-85]. Changing the shape of GNPs to nanorods [80], nanocages [81] or nanoshells [82] shift the absorption to the near infra red (NIR) region (650 – 900 nm); however only spherical GNPs absorb the light in the visible spectrum [82]. Here in **Figure 4**, we enlighten the different gold nanometric shapes and their behavior in the presence of near infra red (NIR) region which suggest their role in photothermal cancer therapeutics. GNPs can be synthesized using a variety of chemical [89-93] and electrochemical synthesis methods [94,95]. We illustrate here some recent developments in synthesis of GNPs that were particularly studied in cancer targeting. In one of the approaches, Angelatos *et al.* incorporated gold nanospheres into a microcapsule shell, which was subsequently doped with GNPs and FITC-dextran in different layers by using layer-by-layer (LBL) technique [96]. It was shown that the FITC-dextran dye, as a model macromolecular payload, could be released in a controlled manner due to rupture of layers of shell upon NIR irradiation. Later on, Skirtach *et al.* used a similar strategy for the delivery of encapsulated material to the cancer cells using polyelectrolyte based layered capsules [97].

5. Gold nanocages in cancer diagnosis and therapy

Gold nanocages (GNCs) are hollow nanometric shape with porous walls that can easily be prepared via galvanic replacement reaction between silver nanocubes and chloroauric acid [98]. Large cross sections of GNCs available for absorption of light in the NIR region along with the scattering property make them excellent prospective imaging contrast agents for cancer diagnosis. This integrated property of GNCs was successfully evaluated in photo-acoustic mapping of sentinel lymph nodes (SLN) [98]. Optical resonance peaks can precisely be tuned into the NIR region by GNCs and, consequently, the adsorption caused by blood components or soft tissues are essentially insignificant. So, the inherent characteristic of GNCs allows strong NIR absorption, which makes them attractive novel theranostics for contrast imaging and photothermal treatment of cancer [99]. Such photo-acoustic mapping of SLN is most often used in breast cancer subjects to evaluate the spreading of cancerous state to the normal cells from the primary tumor [99].

The phenomena of light scattering or absorption are commonly seen when incident photons interact with GNCs [98]. With respect to the prospective of GNCs in cancer therapy, the absorption of incident photons is especially important.

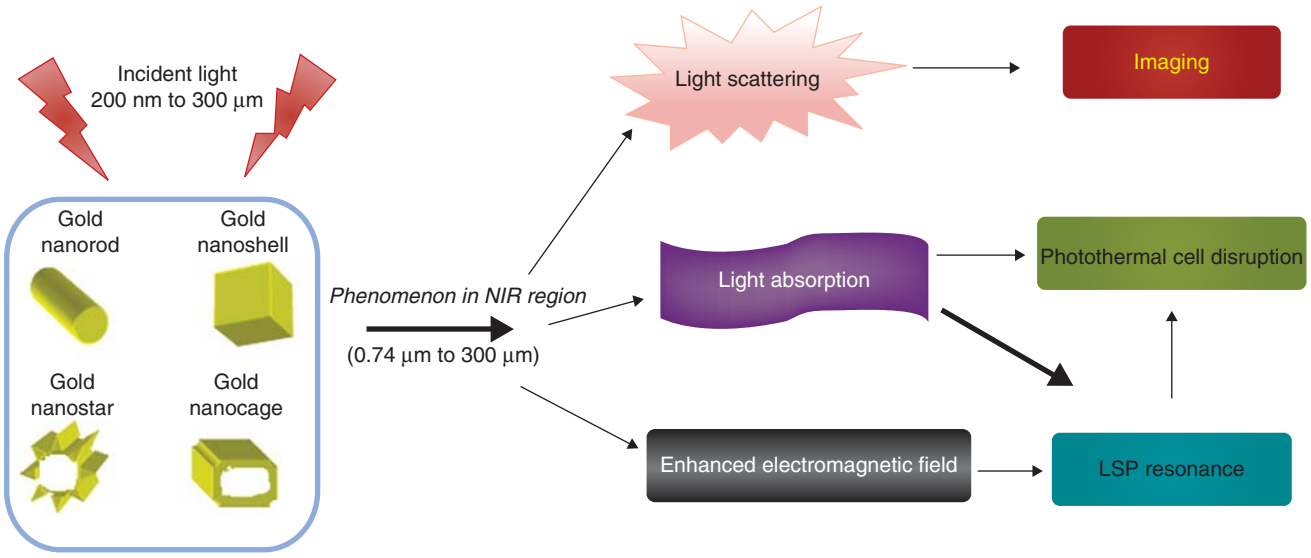

Figure 4. Optical, electrical and thermal effects resulting from irradiation of different gold nano-shapes with NIR irradiation.

The absorbed photons lead to the positional vibration in the lattice of GNCs subsequently raises the surrounding temperature due the exothermic reversal of the lattice. In biological systems where water offers high thermal conductivity, the GNCs produce a local rise in temperature that forms the basis of photothermal cell selective cytotoxicity GNCs. Such photothermal therapy is less invasive than chemotherapy and holds promise as a new form of sole or adjuvant approach for cancer treatment [100]. In this accordance, Chen *et al.* reported the significant raise in the surface temperature of tumor (up to 54°C) in very short span of time (2 min) when PEG coated GNCs that had been accumulated in the tumor region were exposed to NIR light [101]. The same investigators developed anti-HER2 (monoclonal Invitrogen, 28-0003Z) conjugated GNCs as immuno gold nanocage to effectively target HER-2 positive tumors [87].

Potential diagnostic property as another important feature of GNCs was demonstrated by many investigators. Recently, Yang *et al.* ascribed the GNCs as a potential NIR contrast imaging agent for photo-acoustic tomography (PAT) [102]. By imaging the rat cerebral cortex as model tissue, it was found that optical contrast could be enhanced almost two-fold, which lasted for over 5 h [102].

6. Gold nanoshells in cancer diagnosis and therapy

Like GNCs, nanometric shell shape gold (Gold nanoshells; GNSs) exhibit the similar photothermal property in NIR region and form the basis of its photothermal cancer therapy.

GNSs are optically tunable GNPs consisting of a thin metallic gold shell and dielectric core that can easily be tailored to scatter or absorb light depending on the core size and shell dimensions [103]. Having the similar characteristic of absorption and scattering of light like GNCs, GNSs also hold great potential as cancer theranostic materials. GNSs are strong absorber of photons in the NIR region (650 – 900 nm). For the first time, use of nanoshells in photothermal ablation of tumors was shown by Hirsch *et al.* in SKBr3 human breast epithelial carcinoma cells [26]. More recently, O'Neal *et al.* reported a very prospective finding in support of effective photothermal treatment of cancer by GNSs with NIR irradiation. In the CT26 colon carcinoma tumor model in mice complete restoration of the tumors was observed in the PEGylated gold nano-shell treatment mice group within 10 days of treatment. Over the period of 90 days after treatment, all gold nano-shell treated mice were healthy and free from tumors. Baek *et al.* investigated the effects of exposure to laser NIR on multicell human glioma spheroids infiltrated with PEGylated silica coated GNSs loaded macrophages [104]. They reported that macrophages could efficiently take up bare or coated (PEGylated and silica) GNSs. When such GNSs-pre-treated macrophages subsequently infiltrated into glioma spheroids, NIR laser irradiation of the spheroids resulted in complete growth inhibition in an irradiance dependent manner [104]. These findings demonstrate the potential of macrophages as unique kind of delivery vector of GNSs for photothermal therapy of gliomas.

In order to increase the tumor specificity of GNSs, antibodies conjugated NCSs against over-expressed oncoproteins have been investigated in recent time [86]. Anti-HER2 conjugated gold NCSs were developed as theranostic that accumulated in high concentration in breast cancer cells [103]. NIR irradiation of SKBr3 cells that had been pre-treated with such anti-HER2 functionalized nanoshells showed clear circular cell death region corresponding to the spot size of the laser [105]. Utilization of short peptides in enhancing the cell targeted uptake of NP is the recent

biomedical interest in nanomedicine research. GNSs functionalized with a peptide (A54, a 12 amino acid motif) directed to Liver cancer cells were designed and synthesized for photothermal therapy of hepatocarcinoma [106]. They reported that functionalized gold nanoshells showed good targeting ability to liver cancer cells BEL- 7404 and BEL-7402 while normal liver cells (i.e., HL-7702 cells) were avoided. The fluorescence images showed that the gold nanoshells caused liver cancer cells death. These gold nanoshells hold a great promise as delivery agents for the selective photothermal treatment of liver cancer cells [106]. Li *et al.* reported the use of backward-mode photoacoustic microscopy (PAM) for noninvasively imaging of the extravasation of nanoshells within solid tumors. PEGylated nanoshells with a peak optical absorption at approximately 800 nm were intravenously administered. After injection, the accumulated nanoshells delineate the tumor position. Nanoshells accumulation is heterogeneous in tumors: more concentrated within the tumor cortex and largely absent from the tumor core [107]. Bickford *et al.* demonstrate the use of HER2-targeted gold nanoshells for imaging of SK-BR-3 breast cancer. This work validates the proof of concept that nanoshells targeted to extracellular biomarkers can be used to enhance cancer diagnostic imaging for use in point-of-care applications [108]. Fales *et al.* reported the evaluation of surface-enhanced Raman scattering label-tagged gold nanostars, coated with a silica shell containing methylene blue photosensitizing drug for singlet-oxygen generation. The gold nanostars were tuned for maximal absorption in the near-infrared (NIR) spectral region and tagged with a NIR dye for surface-enhanced resonance Raman scattering (SERS). Upon 785 nm excitation, SERS from the Raman dye is observed, while excitation at 633 nm shows fluorescence from methylene blue. Methylene-blue-encapsulated NPs showed a significant increase in singlet-oxygen generation as compared to NPs synthesized without methylene blue. This increased singlet-oxygen generation furthermore showed cytotoxic effects on BT549 breast cancer cells upon laser irradiation. The combination of SERS detection (diagnostic) and singlet-oxygen generation (therapeutic) into a single platform provides a potential theranostic agent [109]. Park *et al.* demonstrated the use of intrinsic two-photon induced photoluminescence (TPIP) to study the cellular level biodistribution of GNSs and GNRs. They reported that GNSs and GNRs had a heterogeneous distribution with higher accumulation at the tumor cortex than tumor core. These GNPs were also observed in unique patterns surrounding the perivascular region. While most GNSs were confined at the distance of approximately 400 μm inside the tumor edge, GNRs were shown up to 1.5 mm penetration inside the edge [110]. Therapeutic capabilities of core-shell NPs composed of a superparamagnetic iron oxide (SPIO) core and a gold shell (SPIO@GNS) were reported by Melancon *et al.* In this study the magnetic/optical properties of SPIO@GNS were examined both in an agar gel phantom and *in vivo* by evaluating contrast-enhanced magnetic resonance imaging (MRI) and by measuring near-infrared (NIR) light-induced temperature changes mediated by SPIO@GNS. In addition, the biodistribution and pharmacokinetics of Indium-111labeled SPIO@GNS after intravenous injection in mice bearing A431 tumors were evaluated. In agar phantoms containing SPIO@GNS, a significant contrast enhancement in T2-weighted MRI was observed and a linear increase in temperature was observed with increasing concentration and laser output power when irradiated with NIR light cantered at an 808 nm. *In vivo*, T2*-MRI delineated SPIO@GNS and magnetic resonance temperature imaging of the same tumors revealed significant temperature elevations when intratumorally injected with SPIO@AuNS and irradiated with NIR light [111]. Wu *et al.* reported the formulation and evaluation of GNSs with a hollow silica core for drug loading and cancer therapy. The silica shells were synthesized using nanoliposome templates, and then GNSs were grown on the outer surface of the silica shells. For therapeutic purposes, doxorubicin (DOX) was incorporated into these NPs. DOX-loaded GNSs killed cancer cells with high therapeutic efficacy when irradiated with near-infrared light, suggesting that the GNSs delivered both DOX and photothermal therapy with a synergistic effect [112].

7. Gold nanorods in cancer diagnosis and therapy

Gold nanorods (GNRs) are an attractive as NIR resonant contrast agents: their synthesis is relatively straightforward and reproducible, and their plasmon resonances can be tuned as an approximately linear function of their aspect ratios. GNRs support a higher NIR absorption per unit volume than most other nanostructures and have narrower line widths than nanospheres at comparable resonance frequencies [113]. The efficient NIR absorption of GNRs has enabled the development of novel modes of contrast for nonlinear optical microscopy, and also various types of optical imaging modalities for deeper penetration into biological tissue conversion. When exposed to higher laser fluencies, GNRs can mediate intense photothermal effects and inflict localized injury on nearby cells [114-117] and tissues [116-118]. Geometry and surface properties of GNPs also influence the biodistribution of GNPs across biological barriers [119]. For example, cellular uptake and biodistribution of gold nanorods (GNRs) surface functionalized with the cyclic RGDfK peptide was reported by Gormley *et al.* The GNRs were synthesized to have a surface plasmon resonance (SPR) peak at 800 nm and grafted with a thiolated PEG corona; The RGD targeting ligand was appended to the distal end of the PEG tails. Active targeting of the RGDfK surface-modified GNRs was confirmed *in vitro* by viture of selective binding and uptake to integrin receptors on angiogenic endothelial cells [120]. Choi *et al.* developed a very effective hyperthermia system for successful photothermal cancer therapy. In this investigation GNRs were loaded into photopolymerized nanogels that could provide stable storage of GNRs and passive delivery to

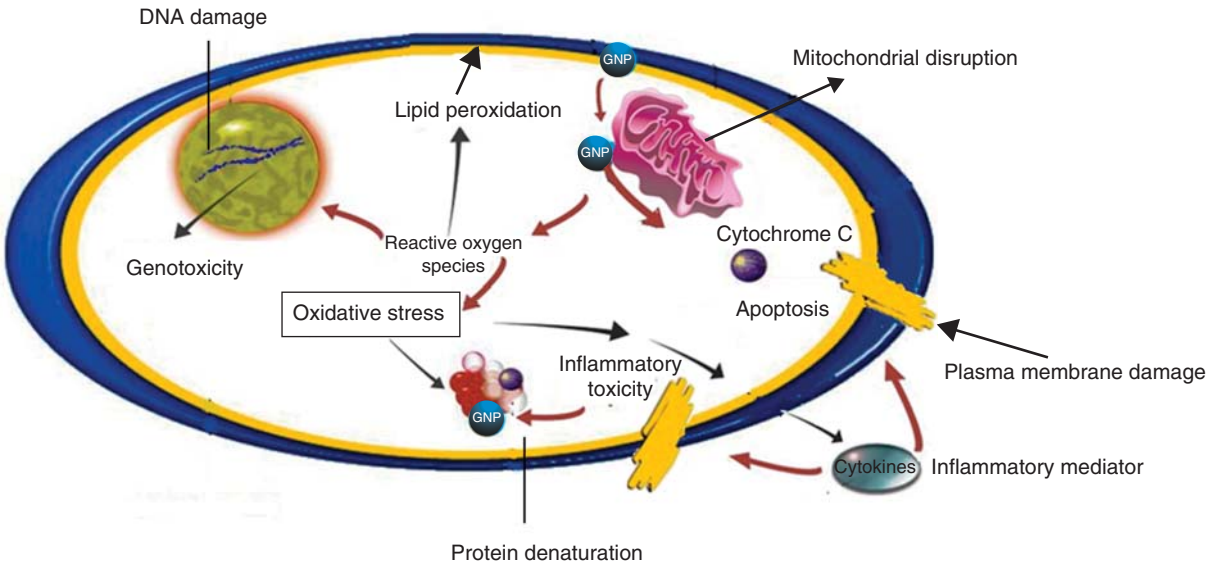

Figure 5. Figure illustrating the toxicity induced by GNPs to different cellular components. GNPs can trigger oxidative stress by formation of intracellular reactive oxygen species (ROS) which can interact with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated damage that leads to mitochondrial damage and cell death by necrosis.
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tumors. An intravenous injection of this system followed by NIR laser irradiation to the tumor site resulted in a very efficient thermolysis in mice bearing squamous cell carcinoma (SSC7) [121]. A single-step layer-by-layer procedure to functionalize GNRs via electrostatic self-assembly was reported by Kirui *et al.* [122]. First, the surface of GNRs was coated with t the cationic surfactant cetyltrimethylammonium bromide (CTAB). A second coating layer of negatively charged polyacrylic acid (PAA) was bound electrostatically. This approach allows for consistent biomolecule coupling to the PAA layer, using standard carboxyl-amine conjugation chemistry. In this investigation GNRs were conjugated to a single-chain antibody A33scFv selective for colorectal carcinoma cells. Uptake and phototermally induced killing of antigen-expressing SW1222 cells were demonstrated using fluorescence microscopy. Selective photothermal therapy was demonstrated using SW1222 cells, where > 62% cell death was observed after cells are treated with targeted functionalized GNRs. Jang *et al.* developed GNRs comnplexed with the photosensitizer aluminium phthalocyanine (AlPcS) [123]. Tumor growth was reduced by 79% with photodynamic therapy PDT alone and by 95% with dual photothermal therapy photodynamic therapy (PDT). This novel multifunctional nanomedicine may be useful for near-infrared fluorescence imaging and PTT/PDT in various cancers [123]. Li *et al.* [124] investigated the conjugation of GNRs with transferrin for efficient targeting, two-photon luminescence imaging and enhanced microsurgery of cancer cells. They observed that gold nanorods are a hundred times more efficient than fluorescein isothiocyanate (FITC) due to due to the large two-photon excitation cross section of GNRs.

8. Toxicity concerns with gold nanomaterials

The therapeutic application of gold materials dates back to classical history; one therefore would favor the biocompatible nature of GNPs. However, since nanomaterials display such tremendously altered properties, one should carefully consider safety/toxicity issues of GNP at both vital organ levels and at cellular levels. In this section, with reference to the current update we enlighten the principle beneath toxicity challenges in the course of GNPs clinical prospective. GNPs may be able to enter into the body via gastrointestinal tract absorption, through the intranasal absorption, systemic injection in to the blood and even by trans-dermal route [125]. Moreover, GNPs may penetrate the small capillaries irrespective of the tissues and efficiently distribute to certain tissues. GNPs passing through epithelia and biological membranes can potentially affect the physiology of cell (**Figure 5**) [2].

Chen *et al.* evaluated the size-associated toxicity and lethality of GNPs over prolonged expose [126]. It was found that particles ranging from 8 to 37 nm induced severe systemic adverse effects in the animal model such as loss of appetite, weight loss and fur color changes. Moreover, death rates of mice exposed to that particular size range were almost total [126]. However, very small GNPs with sizes of 5 nm or bigger particles of 50 and 100 nm were found to be non-toxic [126]. The nontoxic effect of the very small GNPs may be due to the increase in antibody response that enhanced the scavenging effect, resulting in faster clearance of the GNPs [126]. In case of GNPs having the size of 50 nm or larger, the deaths of animal were not seen. It's expected that *in vivo* aggregation of GNPs may have occurred to increase

the apparent particle size and lead to the retardation of cellular uptake [127]. This finding was consistent with the observation that the cell membrane prevents the permeation of particles larger than 200 nm [127].

Alongside the size dependent toxicity, shape, surface coating and charge also play a key role in GNPs associated toxicity [128-131]. Wang *et al.* demonstrated the effect of shape on toxicity and found that rod-shape GNPs were more toxic than spherical GNPs to human HaCaT keratinocytes [128]. This result underscores that it is relevant to distinguish between the toxicity of GNPs core material and on toxicity associated with the surface geometry of the GNPs. It was furthermore found that among the cationic (amine) and anionic (carboxyl) spherical GNPs, positively charged GNPs exhibited more toxic effect than negatively charges particles of the same size [130]. Hillyer *et al.* reported that GNPs can cross the small intestine by persorption and appreciably distribute into blood, brain, lungs, heart, kidney, liver and spleen [130]. Moreover, GNPs can diffuse into chorionic space of embryos and displaying deformities (illustrated in normal Zebrafish) [131]. Effect of surface coating over interaction of GNPs were also evaluated in many studies and concluded that their effect is dependent of the nature of the coating material. Perreault *et al.* investigated the toxicity of Polyamidoamine (PAMAM) coated GNPs in different models [130]. PAMAM coated GNPs, which exert a positive charge due to the nature of the PAMAM polymer, reduced the cellular metabolic activity in algae and bacterial cells. However, PAMAM coated GNPs showed no change in the mitochondrial activity in mammalian cells [132]. Toxicity testing results on GNPs in general is showing the dependency of toxic effects on dose, size, zeta potential and surface functionalization [133]. However, the produced results are not alarming. In our view, the toxicity of gold nanomaterials can be controlled by manipulating surface coating and geometry of the NPs.

9. Expert opinion

GNPs can meet the need for nanocarrier systems in cancer therapy and diagnosis. In cancer therapy, GNPS can be used applied either for drug targeting and as photothermal heat-generating agents In recent years, significant numbers of studies demonstrate their applications in chemical sensing, biological imaging, and drug delivery and as self cancer theranostic (alone able to imaging and kill the cancer cells). Taken together, GNPs have demonstrated marvellous promise for detection and treatment of cancer. Although achievements have been attained in this subject, many fundamental issues still need careful evaluation, like fabrication immunogenicity, optimization of dose as well as the relationships for size and shape based toxicity. Further clinical investigations will determine the translation of GNPs towards clinical applications.

In our view, GNPs serve as promising self theranostics and multifunctional NPs for cancer therapy. Their photothermal properties, high surface area and tunable surface chemistry contribute to their growing applications as new delivery strategies in oncology research. Moreover, the surface plasmon absorption and photothermal effect of GNPs in NIR region serves as the exceptional optical property that can be used for imaging. Loading of chemotherapeutics and biological drugs onto GNPs is one of the promising future applications of GNPs. Lastly, Although gold nanometric shapes appear much less toxic than many other nanomaterials, the toxicity of these nanomaterials needs to be closely evaluated as both chemical composition as wells as the geometry of the particles influence their toxicity. In conclusion, gold nanomaterials are promising for imaging, diagnostics and therapy for cancer.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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