BIOMEDICAL APPLICATIONS OF GOLD NANOPARTICLES

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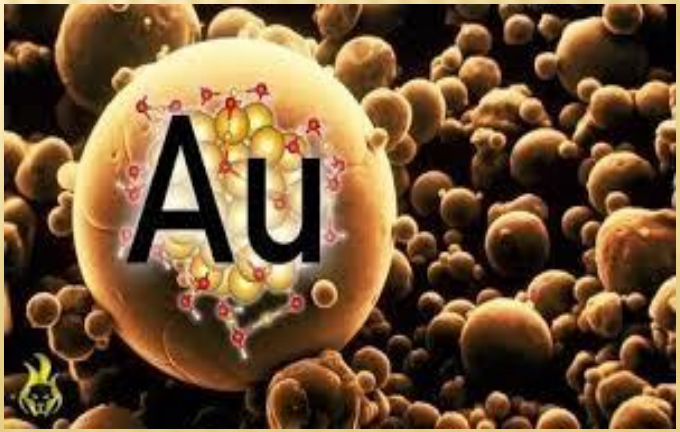
Introduction

- The advent of nanotechnology has increased our capability to engineer the physicochemical properties of materials at the nano-scale to enable their use in various biomedical applications.
- Nanomaterials can be categorized into four types such as: (1) inorganic-based nanomaterials-(AuNPs/CuO); (2) carbon-based nanomaterials (carbon nanotube); (3) organic-based nanomaterials (liposome); and (4) composite-based nanomaterials (any combination of metal-based, metal oxide-based, carbon-based, and/or organic-based).
- Out of all the nanomaterials, gold nanoparticles (GNPs/AuNPs) and silver nanoparticles are the most explored nanostructures for biomedical applications.
- They often find applications in biology and medicine owing to their unique physiochemical and biological properties, including:
  - Small and tailorable size
  - High chemical stability
  - Shape-related optoelectronic properties
  - Eeasy Surface modification
  - Excellent biocompatibility and low toxicity
  - Large surface-to-volume ratio



- AuNPs are typically defined as particles of 1–100 nm in size, which is in the sub-wavelength regime of visible light.

- In particular, they are generally stable against oxidation under physiological conditions (incl. variable pH, ionic strength and temperature) without any major risk of leaching of toxic species.

- The key characteristic that distinguishes AuNPs from many other nanomaterials, in the biomedical context, is their unique optical properties resulting from a physical phenomenon known as localised surface plasmon resonance(LSPR),which is present typically in nanostructures of plasmonic materials, such as gold, silver, copper and aluminium.

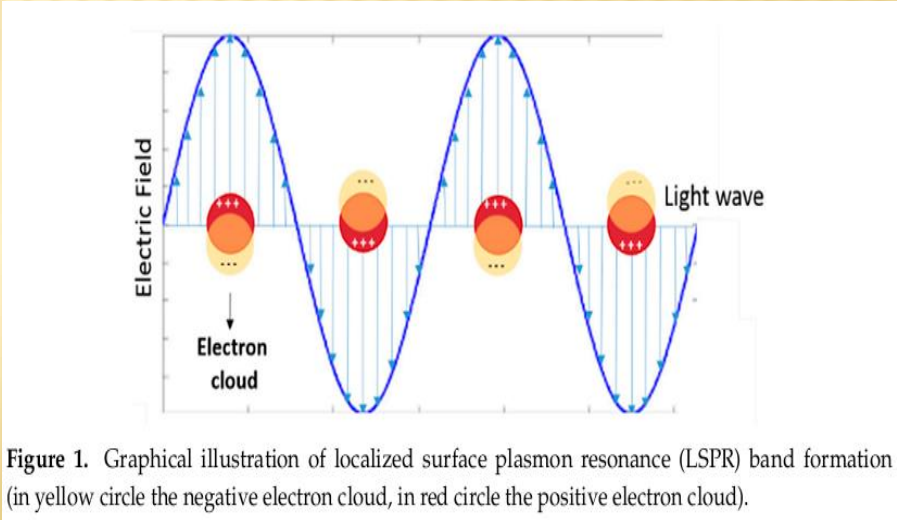
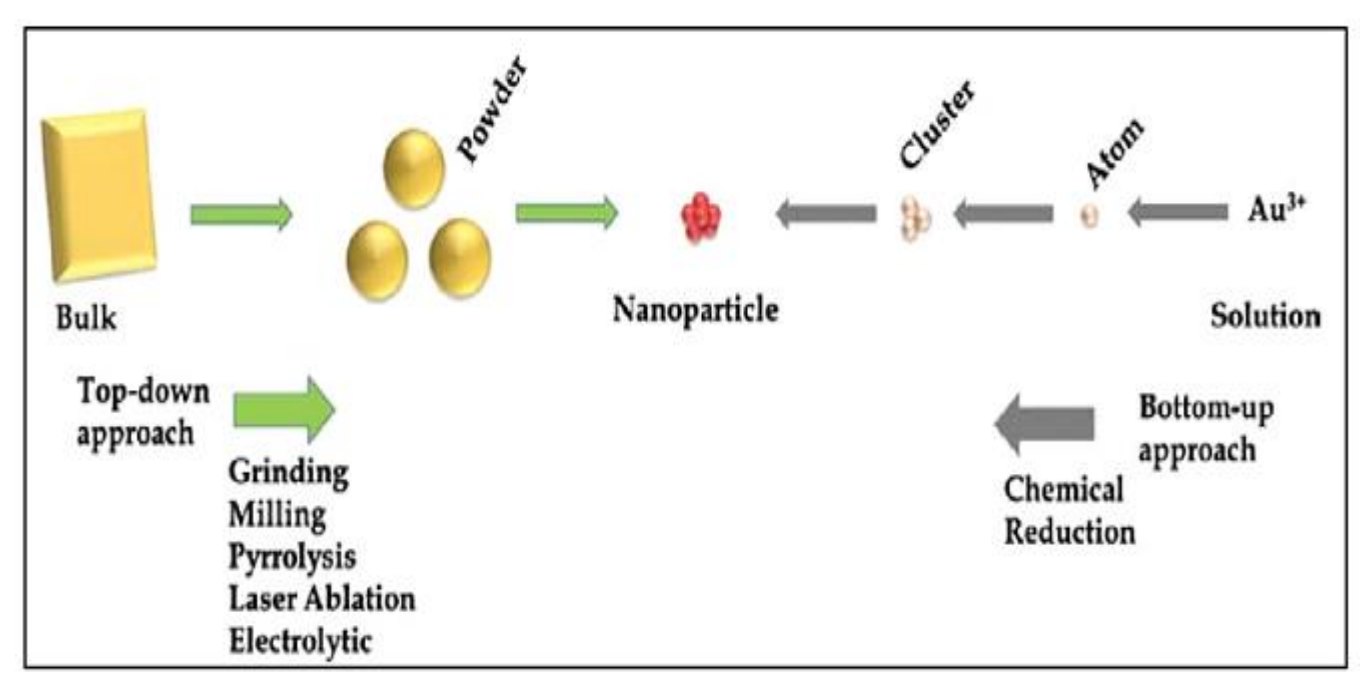


Figure 1. Graphical illustration of localized surface plasmon resonance (LSPR) band formation (in yellow circle the negative electron cloud, in red circle the positive electron cloud).

- These excellent properties of GNPs exhibit their tremendous potential for use including bio-imaging, site specific drug/gene delivery, nano-sensing, diagnostics, photon induced therapeutics, and theranostics.

Synthesis of gold nanoparticles

- To date, there are numerous preparative methods for the synthesis of AuNPs, containing top-down and bottom-up procedures.



- Generally, procedures for the synthesis of Au NPs can be arranged into chemical, physical and biological methods.

1. Methods such as the γ-irradiation method, microwave (MW) irradiation, sonochemical method, ultraviolet (UV) radiation, laser ablation, thermolytic process and photochemical process are categorized as physical procedures.

2. In chemical methods, chemical reactions are performed in an aqueous medium by a reduction agent. Citrate and sodium borohydride are the common reducing agents used.

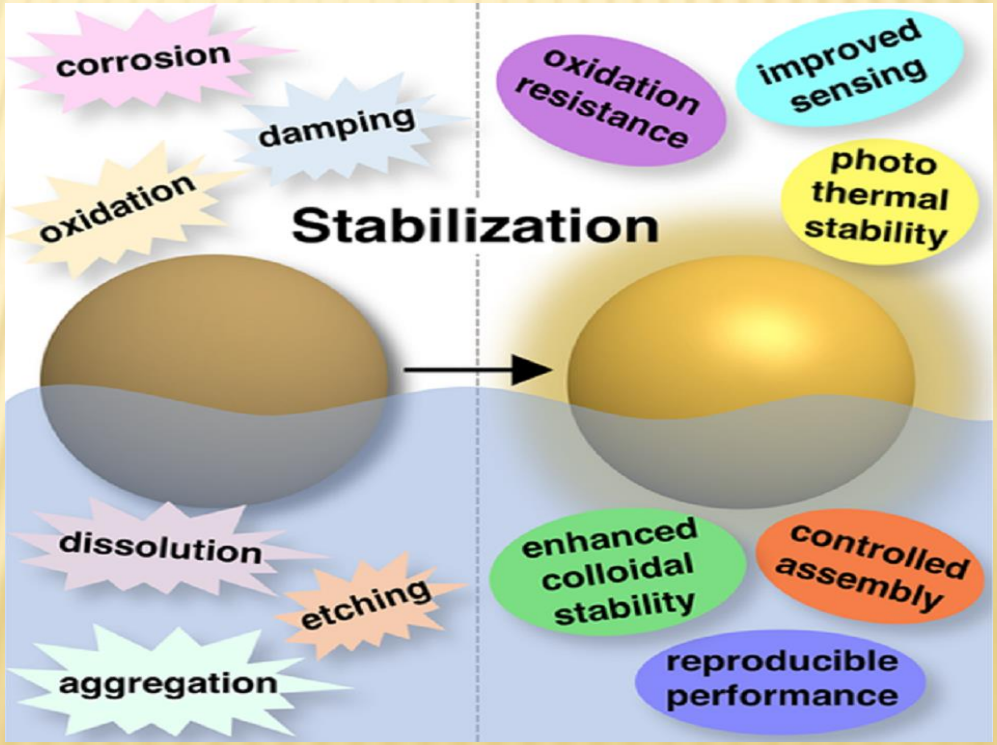
3. Biological synthesis known as favorable environment is another route of synthesis. Reducing hazardous generated wastes and assisting “green chemistry” are the main objectives of biosynthesis. Solvent medium, reducing and stabilizer agents should be nontoxic and safe. Plant-based compounds and derivatives, bacteria, fungi, algae, yeast, and viruses are employed as the common resources.

Table 1
Biological resources for AuNPs synthesis.

Microorganism	Specious Name	Size range (nm)	Shape of AuNPs	Application	Refs.
Plant-based compounds and derivatives	*Panax ginseng*	10–40	Spherical		[38]
	Cacumen platycladi	20–50	Spherical, triangular/hexagonal		[39]
	Plumbago zeylanica	> 100	Spherical, triangles, hexagons	Antibacterial activity against Gram-negative and Gram-positive bacteria	[40]
	Abelmoschus esculentus	45–75	Spherical	Antifungal activity against *Puccinia graminis tritci, Aspergillus flavus, Aspergillus niger* and *Candida albicans*	[41]
	Hibiscus sabdariffa	25–30	Spherical	Selective toxicity towards U87 glioblastoma multiforme cell line under normal and hyperglycemic condition	[42]
	Cucurbita pepo L. leaves	10–15	Spherical		[43]
	Morinda citrifolia	12.17–38.26	Spherical	High potential for use in the treatment of anticancer, antidiabetic	[44]
	Eucommia ulmoides	~20	Spherical	Excellent catalytic activity	[45]
	Trigonella foenum-graecum	15–20	Spherical	Good catalytic activity for the reduction of 4-nitrophenol to 4-aminophenol by excess NaBH4	[46]
	Zingiber officinale	10	Spherical		[47]
	Hibiscus rosa sinensis	~14	Spherical, triangular		[48]
	Rosa hybrida	10	Cubic	High potential for use in biological applications	[49]
	Euphorbia hirta L.	6–71	Spherical	Antibacterial activity of the green synthesized Au NPs against bacterial strains of *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia*	[50]
	Abelmoschus esculentus	62	Spherical	Antifungal activity	[41]
	Cassia auriculata	15–25	Spherical,hexagonal, triangular	May promote anti-hyperglycemic	[51]
	Couroupita guianensis, Aubl.	26 ± 11	Cubic	antioxidant activity	[52]
	Terminalia arjuna.	20–50	Spherical	Enhance the mitotic cell division and pollen germination activity	[53]
	Mentha piperita	> 100	Spherical	Antibacterial activity against clinically isolated pathogens	[54]
Bacteria	*Klebsiella pneumoniae (MTCC- 4030)*	10–15	Spherical	Antibacterial activity against *Escherichia coli*	[55]
	Klebsiella pneumoniae	35–65	Spherical	Medical and pharmaceutical applications	[56]
	Geobacillus sp. strain ID17	5–50	Quasi-hexagonal	Potential application of this microorganism in bioremediation of gold-bearing waste	[57]
	Klebsiella pneumoniae	35–65	Spherical		[56]
	Escherichia coli K12	50	Spherical	Catalytic activity	[58]
	Acinetobacter sp. SW 30	20 ± 10	Triangle, rod, spherical		[59]
	Bacillus stearothermophilus	5–30	Spherical, triangular	Detect toxin A (TOA) of *Clostridium difficile* based on an aptamer	[60]
	Bacillus Subtilis	10–15	Cubic	Antimicrobial agents in packaging applications	[61]
Fungi	*Aspergillus sydowii*	8.7–15.6	Spherical		[62]
	Rhizopus oryzae	43 ± 19	Flower-like	Stable in different physiological buffers and hemocompatible	[63]
	Penicillium citrinum	60–80	Spherical	Antioxidant activity in pharmaceutical and cosmetic industries	[64]
	Alternaria sp.	7–13 and 15–18 and 69–93	Quasi-spherical, Spherical, square, rod, pentagonal, hexagonal		[65]
	Neurospora crassa	32	spherical		[66]
Algae	*Spirulina platensis*	~5	Spherical	Antibacterial activity against Gram positive organisms	[67]
	Turbinaria conoides and Sargassum tenerrimum	27–35	Spherical	Catalytic activator	[68]
	Sargassum swartzii	35	Spherical	Anticancer for HeLa cells	[69]
	Stoechospermum marginatum	18.7–93.7	Hexagonal, triangle	Antibacterial activator	[70]
	Cystoseira baccata (CB)	8.4 ± 2.2	Spherical	Activity in colon cancer cells (cytotoxic effect against colon cancer cells)	[71]
	Tetraselmis kochinensis	5–35	Spherical	Non toxic	[72]
	Kappaphycus alvarezii	10–40	Spherical		[73]
Yeast	*Instant high-sugar dry yeasts*	Dependent on PH	Triangle, truncated triangle, hexagon Nano plates	Plasmonic Properties	[74]
	Yeast extract mannitol (YEM)	4–20	Spherical		[75]
	Baker's yeast (Saccharomyces cerevisiae)	~5.0 ± 2.0	Spherical	Anticancer evaluation against Ehrlich ascites carcinoma cells	[76]
	Hansenula polymorpha	20–40	Spherical		[77]
Viruses	*tobacco mosaic virus (TMV)*	10–40			[78]

Stability of gold nanoparticles

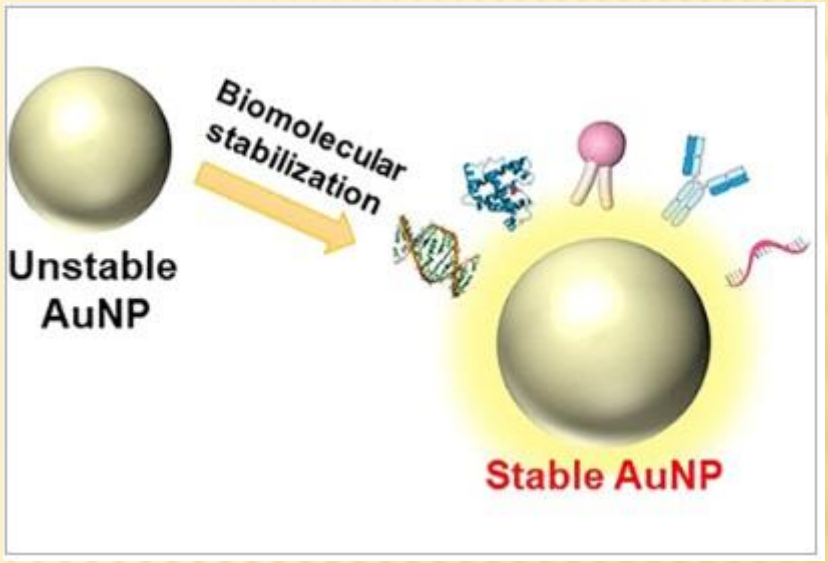
- Bare gold nanopartilces (GNPs) are associated with a few challenges, which need to be resolved to improve the scope of application of GNPs in biomedical engineering. One of the major challenges is to enhance their colloidal stability.(Note that bare GNPs have a natural tendency to agglomerate).

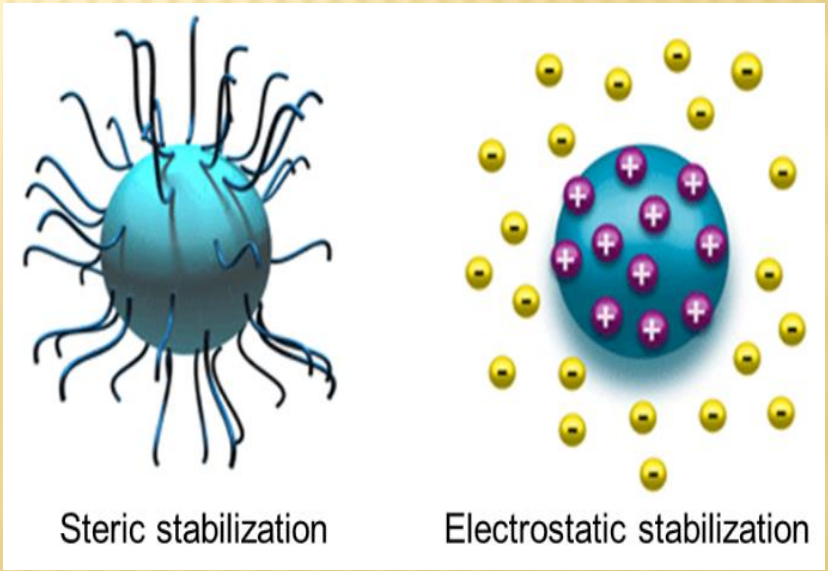


- Colloidal nanoparticles are usually thermodynamically unstable, and hence do not possess good long-term stability primarily as a result of agglomeration.
- The plasmonic properties of metal nanoparticles can change significantly with changes in particle size, shape, composition, and arrangement. Thus, stabilization of the fabricated nanoparticles is crucial for preservation of the desired plasmonic behavior.
- The stability of the GNPs can be improved by a number of techniques/approaches ,e.g., electrostatic stabilization, steric stabilization, phosphine ligation, thiol ligation, and ligand exchange.
- Electrostatic and steric stabilization are the two major techniques used to stabilize nanoparticles in the liquid medium.

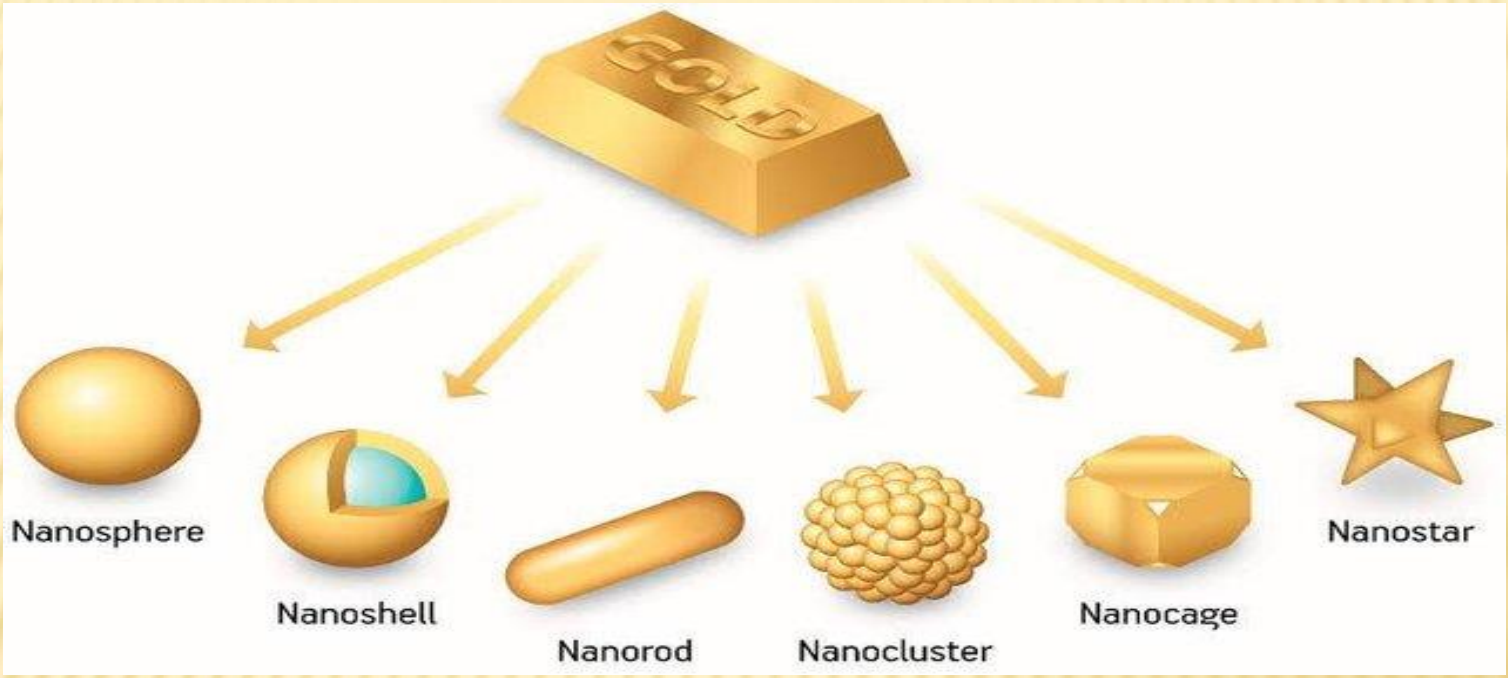
- The steric approach is based on the addition of organic moieties (polymers, surfactant, biomolecules) to the system to be adsorbed onto the particle surface. It works by ensuring that individual Au nanoparticles are not permitted to come into close proximity.

- The electrostatic, or charge stabilization, approach makes use of interactivity between anionic species such as halides or polyoxoanions and co-ordinatively unsaturated atoms present at the surface of the metal, the outcome of which is the creation of a scattered dual electrical layer that facilitates coulombic repulsion among the Au nanoparticles.





Types of gold nanoparticles



- Based on dimensions, AuNPs can be divided into three parts:

I) One-dimensional AuNPs: nanorods, nanowires, nanotubes, nanobelts.

II) Two dimensional AuNPs: gold nanoplates such as stars, pentagons, squares/rectangles, dimpled nanoplates, hexagons, truncated triangle.

III) Three dimensional AuNPs: gold nanotadpoles, gold nanodumbbells (AuNDs), branched AuNPs such as nanopods, nanostars and gold nanodendrites.

As the pictures indicate, a variety of morphologies and sizes of the nanoparticles have specific optical property. It may turn in both the visible and near-infrared spectrum.

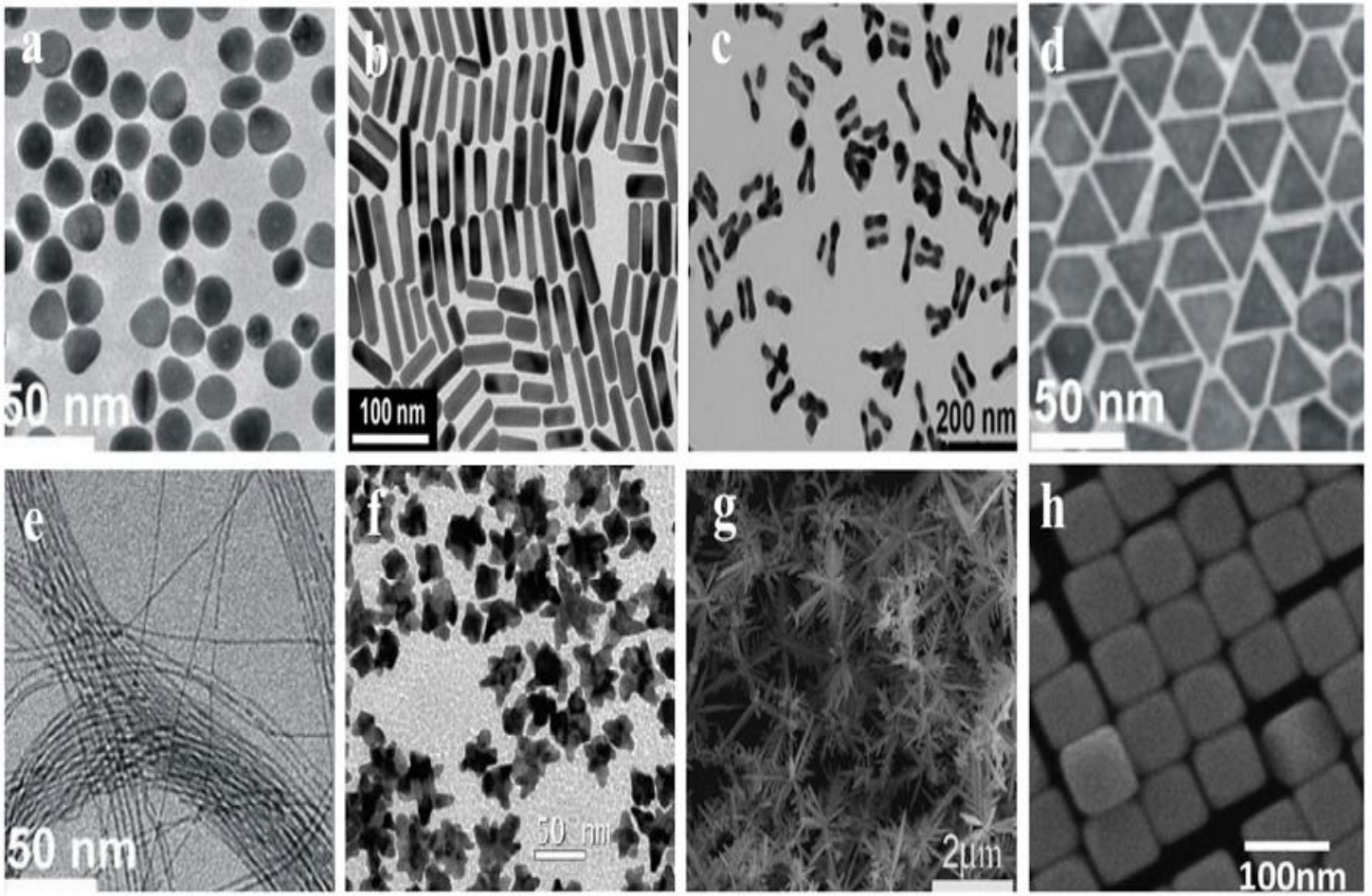


Fig. 1. (a-f) TEM images of AuNPs: a) quasi-spheres [20] b) nanorods [21] c) Nanodumbbells [22] d) triangular nanoprisms [20] e) Ultrathin nanowires [20] f) nanostars [23]; (g-h) SEM images of AuNPs: g) nanodendrites [24] h) nanocubes [25]. Copyright © American Chemical Society.

Properties of gold nanoparticles

- Surface Chemistry

Gold nanoparticles are coated, stabilized, functionalized, or conjugated with different organic moieties to improve their stability or specificity, thereby forming a protective layer on the surface of the particles and preventing aggregation in biological fluids.

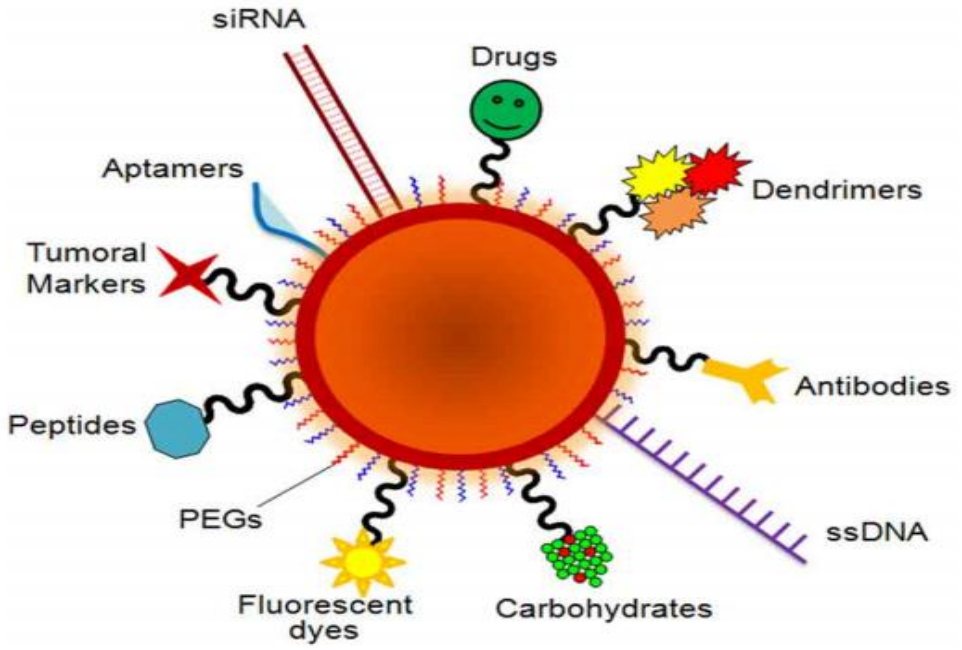


FIGURE 1 | Schematic representation of a multifunctional nanocarrier. These innovative NPs comprise nucleic acids such as RNA and DNA used for gene silencing approaches and in colorimetric assays, respectively. Aptamers and anticancer drug molecules are also used for delivery to the target tissue. Carbohydrates may be useful as sensitive colorimetric probes. PEG is used to improve solubility and decrease immunogenicity. Responsive nanocarriers can also trigger reaction upon external stimuli through the functionality of valuable tumor markers, peptides, carbohydrates, polymers and antibodies that can be used to improve nanocarrier circulation, effectiveness, and selectivity. Multifunctional systems can also carry fluorescent dyes that are used as reporter molecules tethered to the particle surface and employed as tracking and/or contrast agents.

- Physical properties

The intrinsic optical properties of AuNPs provide the opportunity of being composite therapeutic agents in the clinic. The morphology and physiology of AuNPs is associated with optical features. Changing the size of the nanoparticles, affects the color of colloidal AuNPs. This trait utilizes the fundamental of colorimetric detection forms

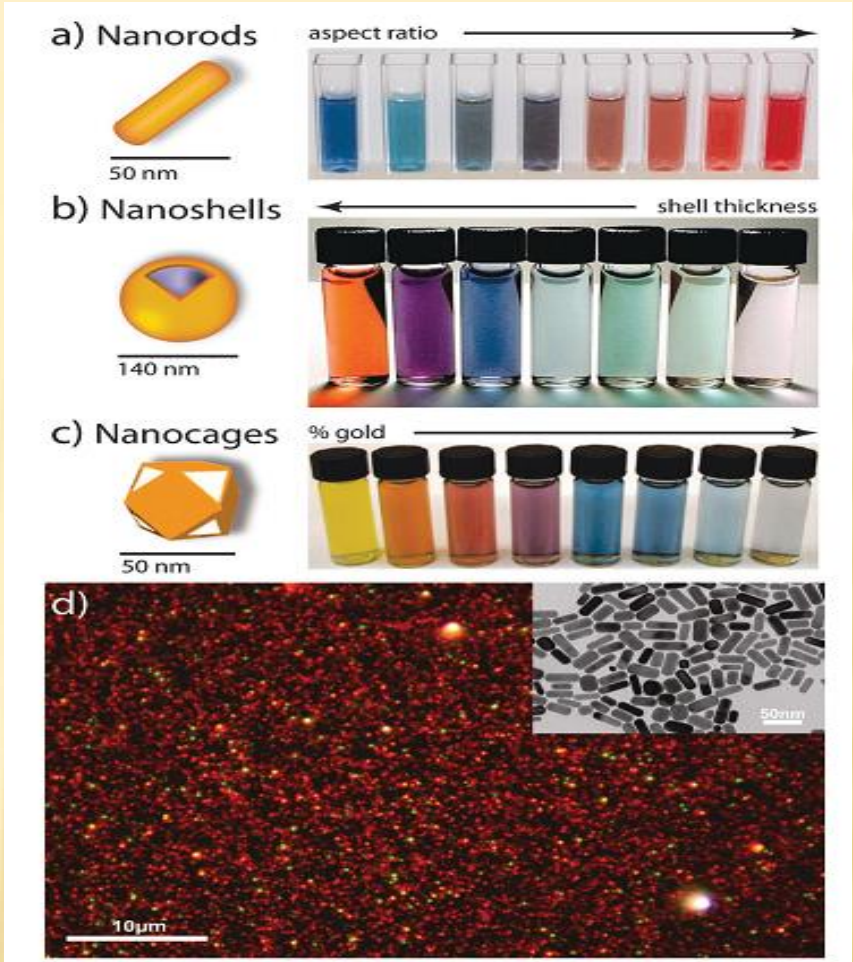
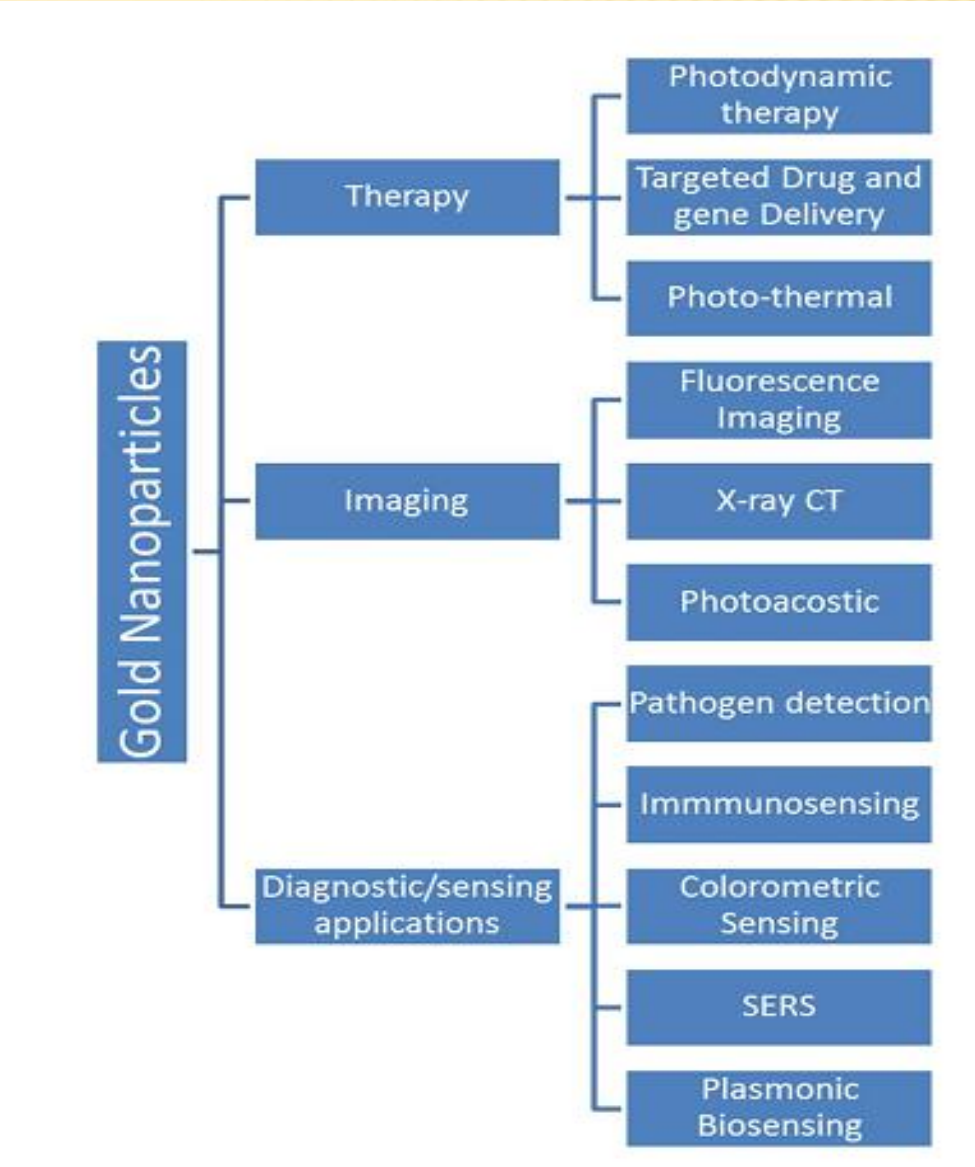


Fig. 2 Gold nanoparticles commonly applied in biomedical applications. (a) Gold nanorods, (b) silica–gold core–shell nanoparticles, and (c) gold nanocages. The intense color of these nanoparticles arises from the collective excitation of their conduction electrons, or surface plasmon resonance modes, which results in photon absorption at wavelengths which varies with (a) aspect ratio, (b) shell thickness, and/or (c) galvanic displacement by gold. (d) Optical dark-field scattering micrograph of gold nanorods (electron micrograph in the inset) showing resonant scattering from their transverse (short-axis) plasmon mode (green) and their lower energy, longitudinal (long-axis) plasmon mode (red)). Image (a) by X. Huang, (b) by C. Radloff and N.J. Halas, and (d) by C. Rosman and C. Sönnichsen. Figures adapted with permission from (b) ref. 7 and (c) ref. 8. Copyright (a) 2003 Annual Reviews and (b) 2007 Macmillan Publishers Ltd.: Nature Publishing Group.

Biomedical applications of AuNPs

- The potential of AuNPs for biomedical purposes has awakened interest owing to their unique optical properties (strong and size-tunable surface plasmon resonance, and fluorescence), easy surface functionalization, and biocompatibility. Some of the important biomedical engineering applications are biomedical imaging, diagnostics, nano-biosensing, nanotheranostics,nanomedicine,targeted cancer treatment, dentistry and photothermal/photodynamic therapy.



1. Bio-imaging applications

- GNPs have been proven to be a better choice for in vivo and in vitro imaging due to low toxicity, low interaction with biological components, easy synthesis, easy surface modification, and easy LSPR tunability.

- The use of GNPs in biomedical imaging techniques such as X-ray computed tomography, photo-acoustic imaging, darkfield microscopic imaging, magnetic. resonance imaging, and fluorescence imaging is very popular.

- GNPs have provided possible solutions to these issues and have many advantages over organic fluorophores and quantum dots.

- The presence of LSPR in GNPs is the main advantage of using GNPs. By varying the size/shape of GNPs, the LSPR wavelength can be tuned from the visible to the NIR region of the electromagnetic spectrum.

- Nanocages have considerably improved the photo-acoustic tomography (PAT). PAT has applications in blood flow monitoring, temperature monitoring, oncology, gastroenterology, neurology, cancer treatment and many more.

- GNPs have good X-ray absorption efficiency and therefore can provide contrast to computed tomography images. Conventional iodine based contrast agents have short circulation time in blood, while GNPs show good circulation time. Excitingly, GNPs have been used in targeted cellular level detection of cancer using specific immunogens.

- Gadolinium based contrast enhancement agents have been widely used to obtain MRI images. The hybrids of gold with gadolinium chelates have also been reported for improved MRI performance. Magnetic nanocores (e.g., iron, cobalt and nickel) coated with gold shells have been successfully used to enhance MRI contrast.

- Gold, when interacting with magnetic nanoparticles, produces magneto-plasmonic properties. These magneto-plasmonic structures have been utilized in MRI contrast enhancement as well as for optical bio-imaging.

Triple-modality detection of brain tumors in living mice with MRI, photoacoustic and Raman imaging.

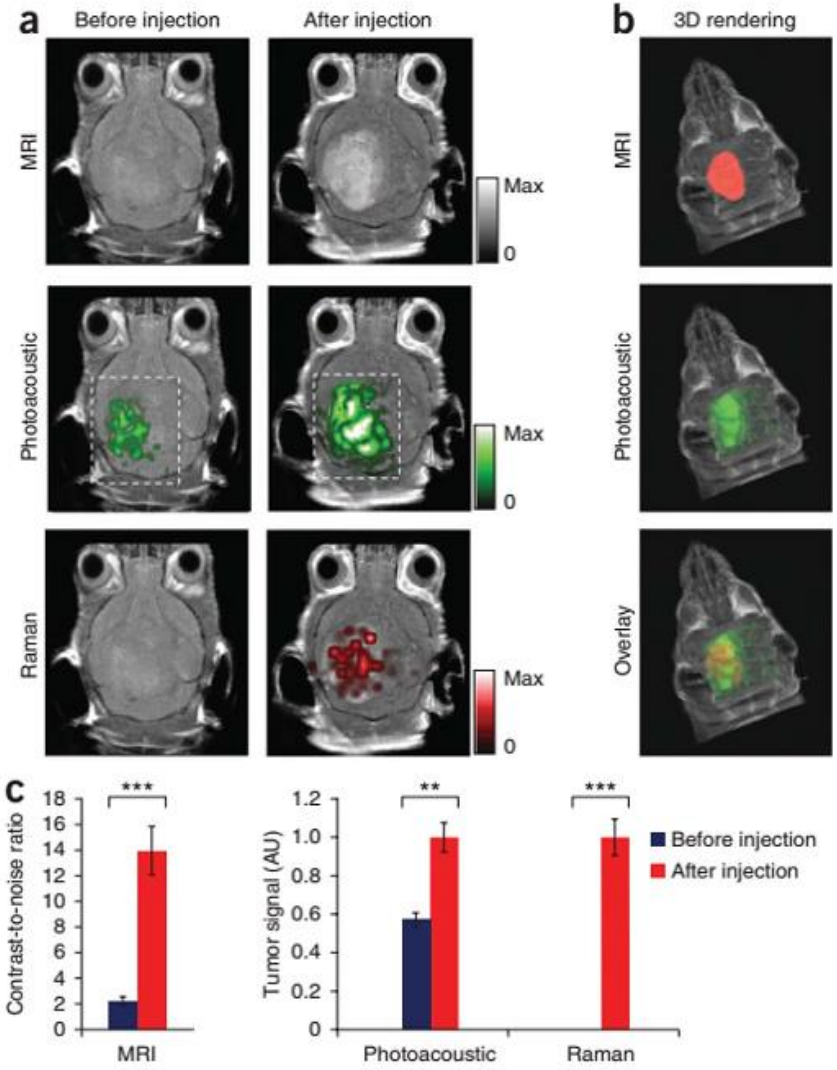


Fig. 11 Triple-modality detection of brain tumors in living mice with MRI, photoacoustic and Raman imaging. (a) Two-dimensional axial MRI, photoacoustic and Raman images. The post-injection images of all three modalities showed clear tumor visualization (dashed boxes outline the imaged area). (b) A three-dimensional (3D) rendering of magnetic resonance images with the tumor segmented (red; top), an overlay of the three-dimensional photoacoustic images (green) over the MRI (middle) and an overlay of MRI, the segmented tumor and the photoacoustic images (bottom) showing good localization of the photoacoustic signal with the tumor. (c) Quantification of the signals in the tumor showing a significant increase in the MRI, photoacoustic and Raman signals after as compared to before the injection. $n = 4$ mice.[244] There are some other bio-imaging methods that use GNPs like the photoluminescence method, dark field optical microscopy, Raman confocal microscopy, positron emission tomography, single positron emission computed tomography and Cerenkov luminescence imaging. All these microscopic techniques have incorporated GNPs in order to have better efficiency.[244] This figure has been adapted/reproduced from ref. 244 with permission from Springer Nature, copyright 2012.

2. Bio-sensing application

- Au NPs have been used as efficient sensors for the detection of different analytes such as metal ions, anions, and molecules like, saccharides, nucleotides, proteins and toxins. Fig. 5 shows various nanobiosensors based on AuNPs features.

- The fundamentals of colorimetric sensing is based on visible color change due to the aggregation of AuNPs,fluorescence-based sensors: the fluorescence quenching feature of AuNPs, electrical and electro-chemical sensors conductivity, high surface area and catalytic propeties of AuNPs, AuNP-based surface plasmon resonance sensors: the optical properties (surface plasmon resonance, SPR) of AuNPs,surface-enhanced Raman scattering (SERS)-based sensors: the inelastic scattering of photons by AuNPs.

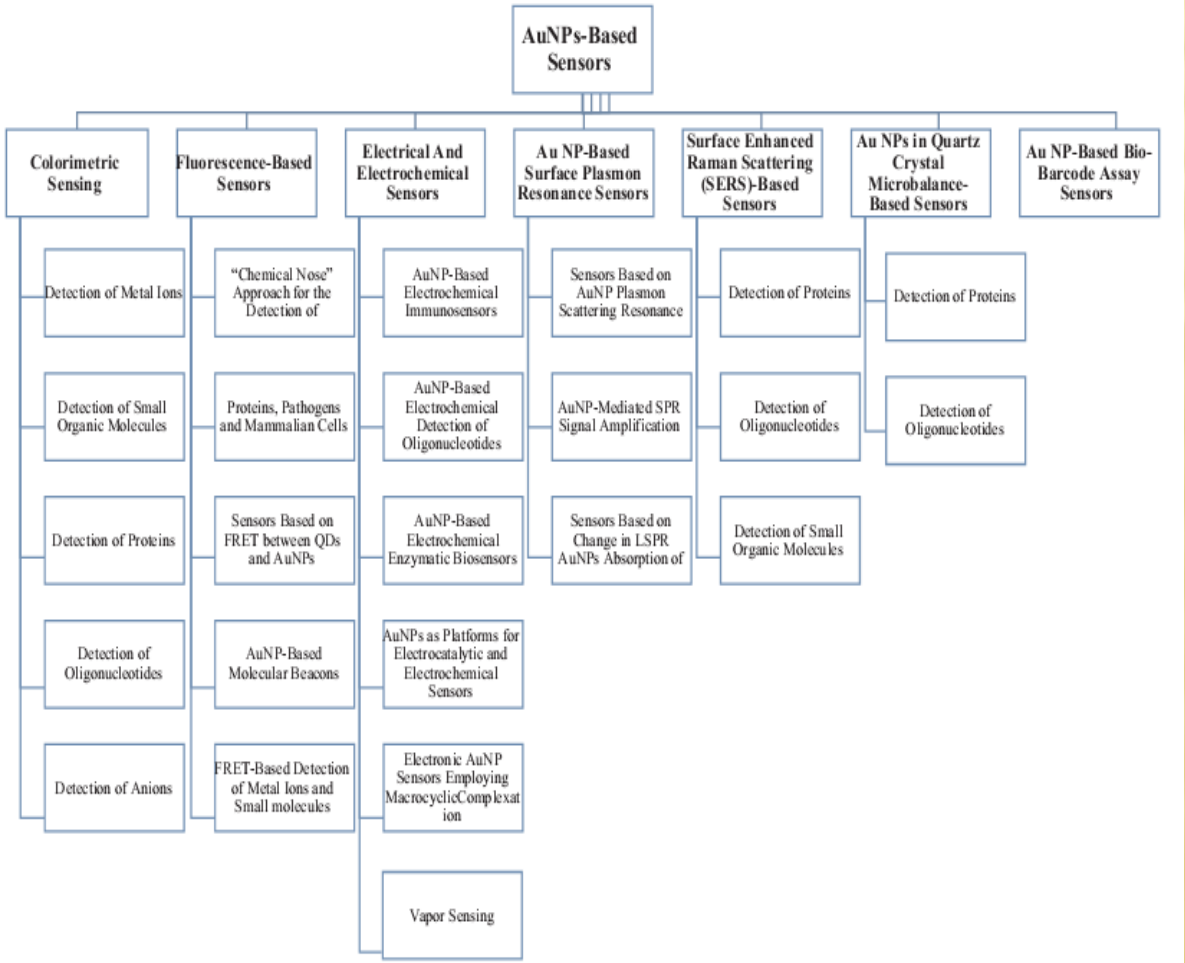


Fig. 5. Summary of different types of gold nanoparticles biosensors; utilizing the explicit physicochemical properties of this nanoparticles, various sensors can be designed.

A polyA aptamer-based label-free colorimetric biosensor for the detection of kanamycin in human serum.

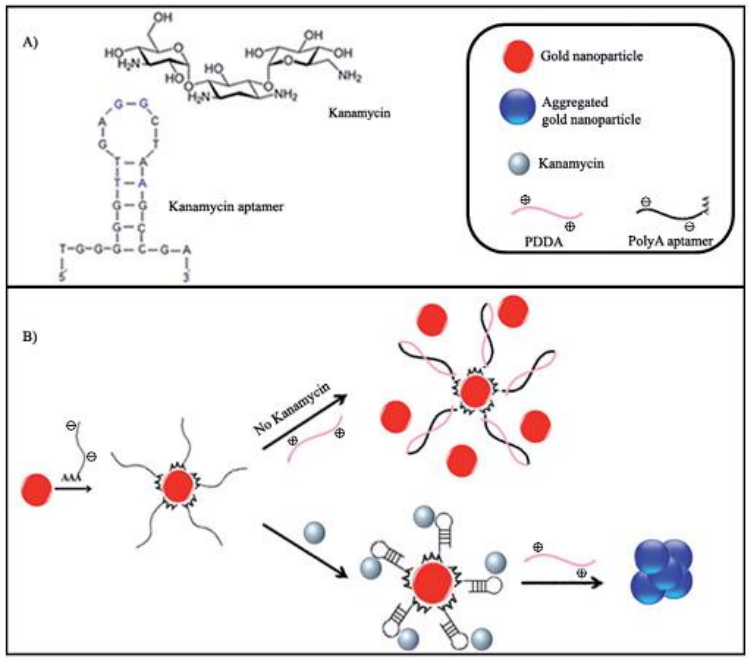
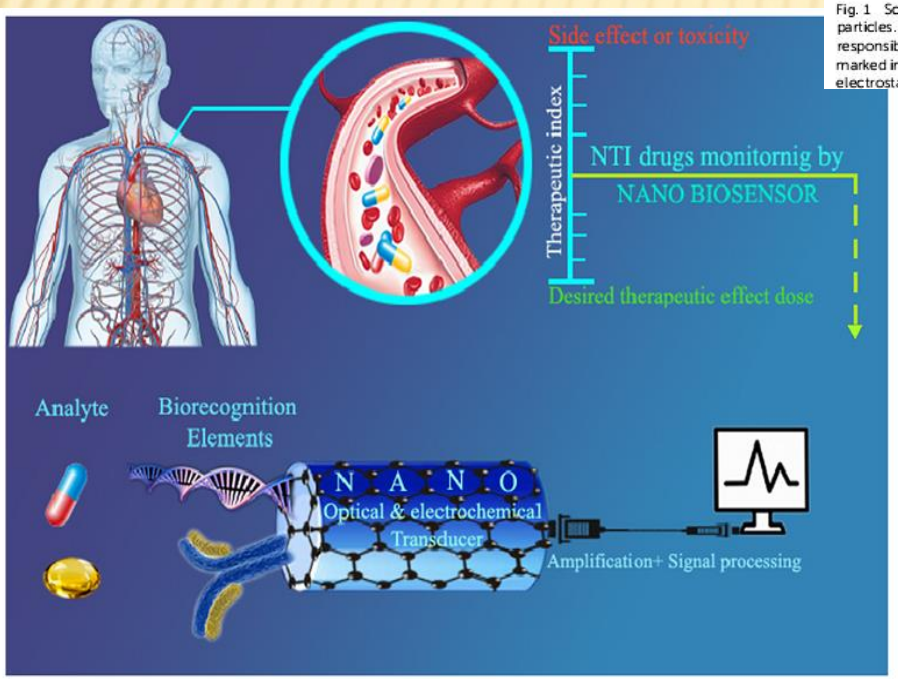


Fig. 1 Schematic illustration of the colorimetric detection of kanamycin based on the interaction between a polyA aptamer and gold nanoparticles. (A) The chemical structure of KAN and the secondary structure of the ssDNA anti-kanamycin aptamer. The aptamer sequence responsible for the binding of KAN has been reported to be the "–TA–" and "–GG–" regions in the stem and loop, respectively[26] (these regions are marked in blue). (B) In the absence of KAN, PDDA formed the hybrid complex with polyA (that is adsorbed on the gold nanoparticles) by attraction electrostatic force. In the presence of KAN, the aptamer interacts with the KAN and frees the PDDA causing the aggregation of the AuNPs.



Scheme 1 Schematic representation of detection of NTIDs in blood matrix by nano optical and electrochemical sensor and biosensor

Nano optical and electrochemical sensors and biosensors for detection of narrow therapeutic index drugs.

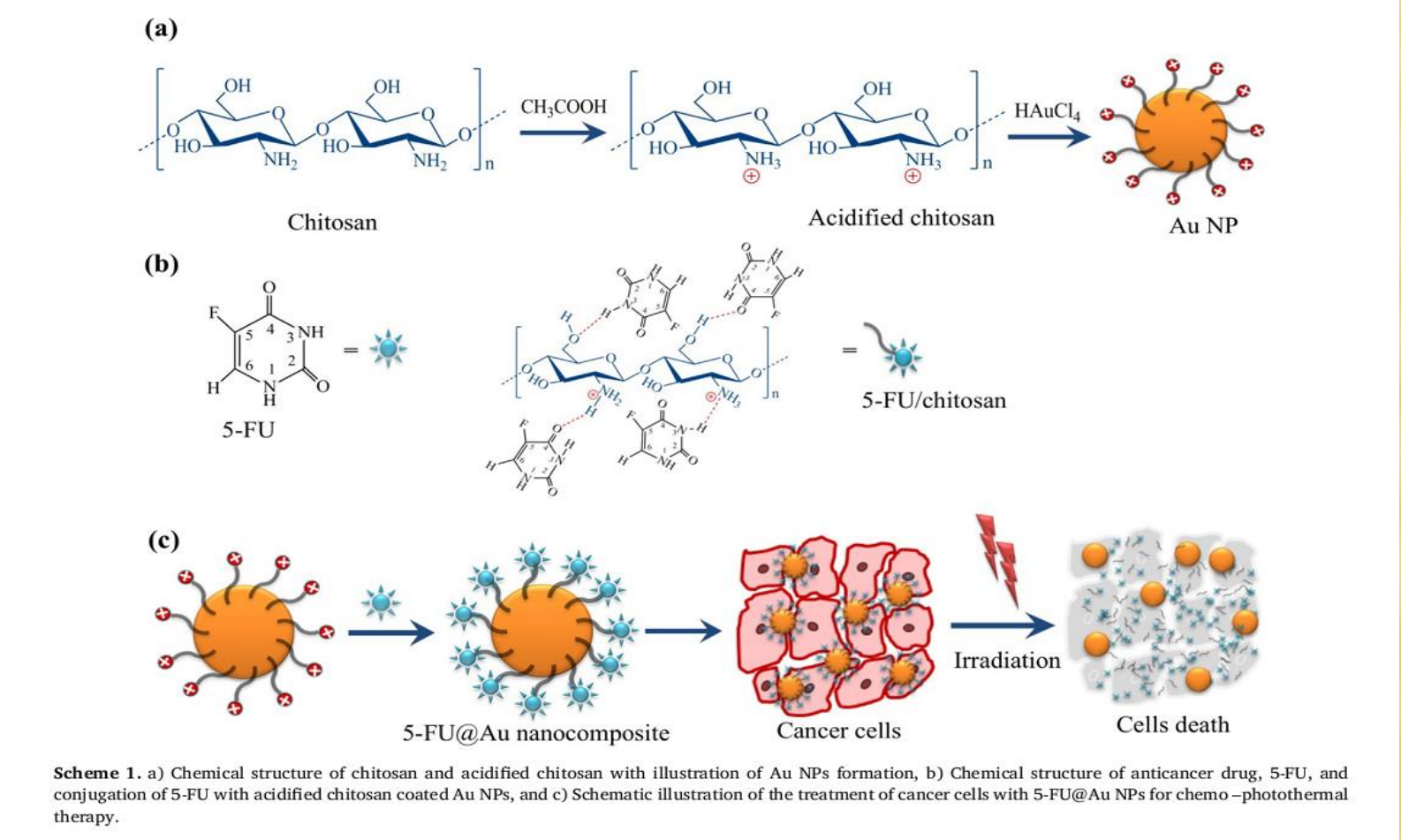
3.Therapeutic applications of GNPs

Table 1
Summary of the potential applications of AuNPs in cancer therapy and suitable types of AuNPs in each modality.

Therapeutic application	Comments	Suitable type of AuNPs
Drug delivery	Surface properties play the most important role in delivery applications; shape is not found to have any effect	Any; most studies have utilized nanospheres
RT	~13 nm nanospheres have been suggested as the optimized size for radiosensitization; shape is not found to have any effect	Any; most studies have utilized nanospheres
PTT	Nanoparticles should be designed to have a strong light absorption in the NIR window; shape can alter the optical properties	Advantages to using nanorods and nanocages; nanoshells and nanocages are appropriate for heat-triggered drug release

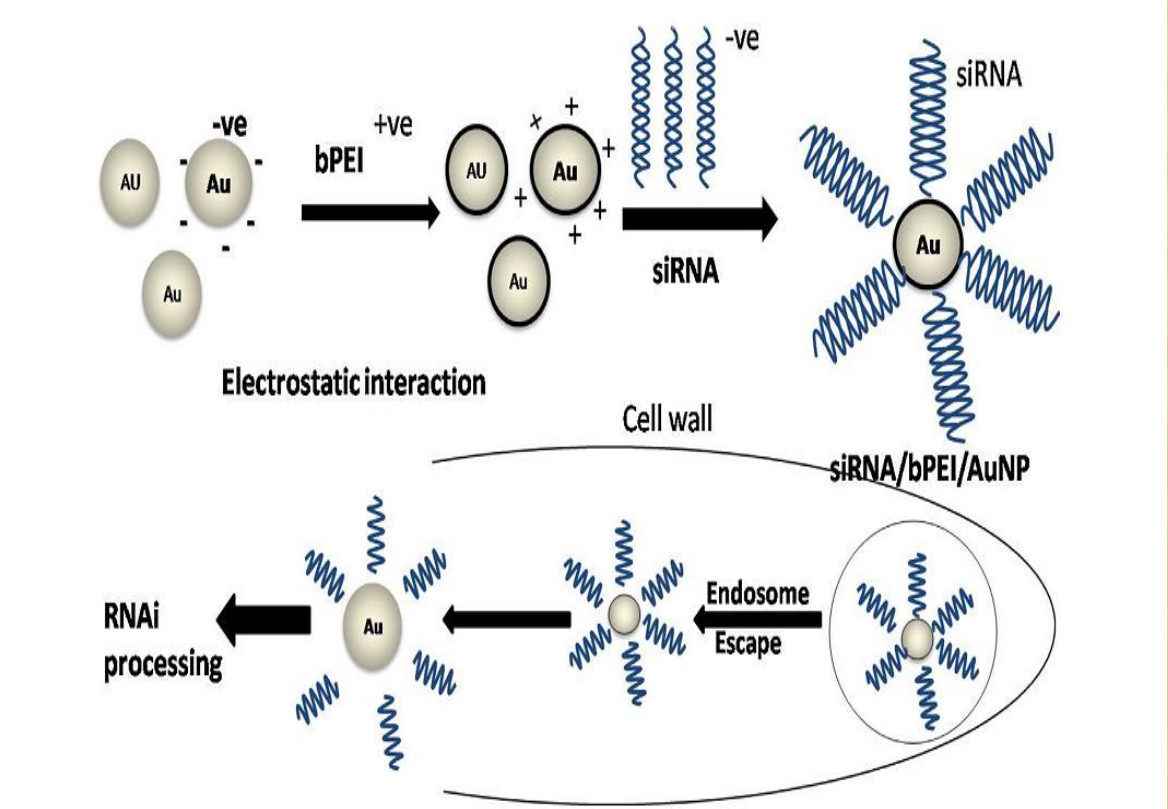
- Drug and gene delivery

Considerable features of AuNPs such as unique optical, physicochemical properties, biocompatibility, functional flexibility, tunable monolayers, controlled dispersity, high surface area for loading the density of drugs, stability and nontoxicity make them an efficient nanocarrier in drug and gene delivery systems.



Scheme 1. a) Chemical structure of chitosan and acidified chitosan with illustration of Au NPs formation, b) Chemical structure of anticancer drug, 5-FU, and conjugation of 5-FU with acidified chitosan coated Au NPs, and c) Schematic illustration of the treatment of cancer cells with 5-FU@Au NPs for chemo –photothermal therapy.

- Gold nanoparticles (GNPs) have shown excellent potential to overcome biological barriers and enhance cellular drug accumulation.
- To overcome the rapid enzymatic degradation and low transfection efficiency of siRNA, the delivery carriers for siRNA is a therapeutic demand to increase its stability. Gold nanoparticles modified by branched polyethyleneimine (bPEI) were developed as an efficient and safe intracellular delivery carriers for siRNA.
- Delivering siRNA efficiently to the target cell/tissue/organ is a challenge, since naked siRNAs is rapidly degraded by serum ribonucleases and have difficulty in passing through the cell membrane, because of their poly-anionic nature and relatively large molecular weight.

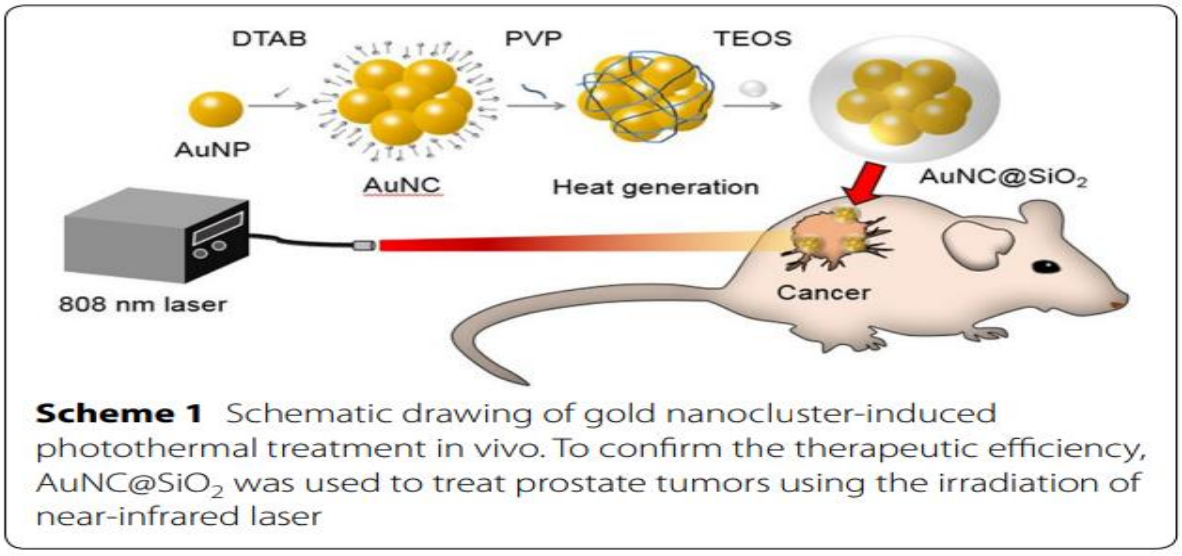


Scheme 1. Schematic illustration of the formation of polyelectrolyte complex siRNA/bPEI/AuNPs by electrostatic interaction between siRNA and bPEI capped AuNPs.

Gold nanoparticles in cancer therapy

- Conventional cancer therapy methods encounter with serious drawbacks and cannot often provide satisfactory outcomes. It has been demonstrated that the effect of various treatment modalities can be enhanced when combined with nanomaterials.

- Recently, gold nanoparticles have been widely implemented as one of the leading nanomaterials for combinatorial cancer therapy.



Scheme 1 Schematic drawing of gold nanocluster-induced photothermal treatment in vivo. To confirm the therapeutic efficiency, $AuNC@SiO_2$ was used to treat prostate tumors using the irradiation of near-infrared laser

- Like other nanoscale materials, AuNPs are able to passively accumulate and preferentially retain at the tumor site via enhanced permeability and retention (EPR) effect arising from the leaky vasculature and ineffective lymphatic drainage of the tumor tissue

- Moreover, the surface of AuNPs can be easily functionalized with active targeting moieties such as proteins, peptides, monoclonal antibodies and small molecules to avoid from non-specific uptake, thus realizing tumor-specific targeting.

- AuNPs with high atomic number provide a larger X-ray absorption cross-section, making them qualified agents to be served as effective radiosensitizers for enhance RT.

AuNPs in cancer chemotherapy

- Precise delivery of nanovehicles to the diseased tissue, controlling the rate and site of payload release, enhancing the bioavailability of drug at the target site, improved solubility and stability of drug are some of the favorable attributes of drug delivery using nanoparticles which may lead to reduced morbidity and mortality rates.

- To date, different kinds of nanocarriers have been used for drug delivery applications such as liposomes, polymers, dendrimers and metallic nanoparticles. AuNPs possess outstanding properties that make them an ideal drug delivery scaffold.

- Owing to high surface area-to-volume ratio, a dense loading of ligands with diverse functions involved in therapy, diagnosis and targeting can be anchored to the surface of AuNPs.

- To develop a drug delivery system, it is necessary to understand how different physiochemical properties such as size, surface charge and surface modification could affect the cellular uptake and intracellular fate of AuNPs.

Table 2
Summary of recent studies on the use of AuNPs in chemotherapy.

Ref.	Cell line/Animal model	Au nanocomplex/Size (nm)	Drug	Results		
				Comparison index	Free drug	Nanocomplex
Morshed et al. [56]	MDA-MB-231 breast tumor	TAT[1] peptide-PEG[2]-AuNPs/23.6	Doxorubicin	Animal survival (days)	25	39
Zhou et al. [59]	4 T1 breast tumor	Au nanoclusters/FA[3]/8.8	Cisplatin	TGI[4] (%)	~45	~82
Labala et al.[63]	B16F10 melanoma cells	LbL[5]-AuNPs/98.5	Imatinib mesylate	Cell viability (%)	41.4	18.5
Tummala et al. [64]	HCT-116 colorectal carcinoma	DSPE-PEG-COOH-anti DR5-AuNPs/91	Oxaliplatin	TGI (%)	~36	~82
				Cell viability (%)	~31	~20
Paciotti et al. [65]	B16F10 melanoma tumor	TNF[6]-PEG-thiol-AuNPs/27	Paclitaxel	TGI (%)	24	62
Kumar et al. [66]	PC-3 prostate cancer cells	GSH[7]-CRGDK[8]-AuNPs/5.2	Platinum(IV)	Apoptosis ratio (%)	~38	~92
Murawala et al. [67]	MCF-7 breast cancer cells	BSA[9]-AuNPs/~50	Methotrexate	Cell viability (%)	~85	~50
Saber et al. [68]	HUVEC[10]	cRGD-chiotosan-AuNPs/50	Sunitinib malate	Cell viability (%)	~47	~30
Yang et al. [69]	MDA-MB-231 breast cancer cells	Pentapeptide-RGD[11]-AuNPs/19	Bleomycin	Cell survival fraction (%)	~60	~18

[1] Trans-activating transcriptional activator.
[2] Poly (ethylene glycol).
[3] Folic acid.
[4] Tumor growth inhibition.
[5] Layer-by-layer polymer: poly(styrene sulfonate) and polyethylene imine.
[6] Tumor necrosis factor alpha.
[7] Glutathione.
[8] Cyclic Arg-Gly-Asp-Lys peptide ligand.
[9] Bovine serum albumin.
[10] Human umbilical vein endothelial cells.
[11] Peptide based on the cyclic Arg-Gly-Asp.

- Radiotherapy (RT)

- Photothermal therapy (PTT)

- Radiofrequency hyperthermia (RFHT)

- Ultrasound-induced hyperthermia (USHT)

- Magnetic hyperthermia (MHT)

- Photodynamic therapy (PDT)

- Sonodynamic therapy (SDT)

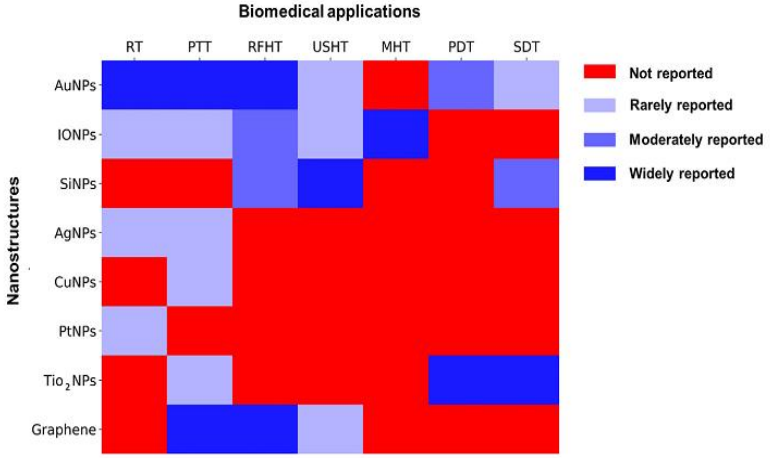
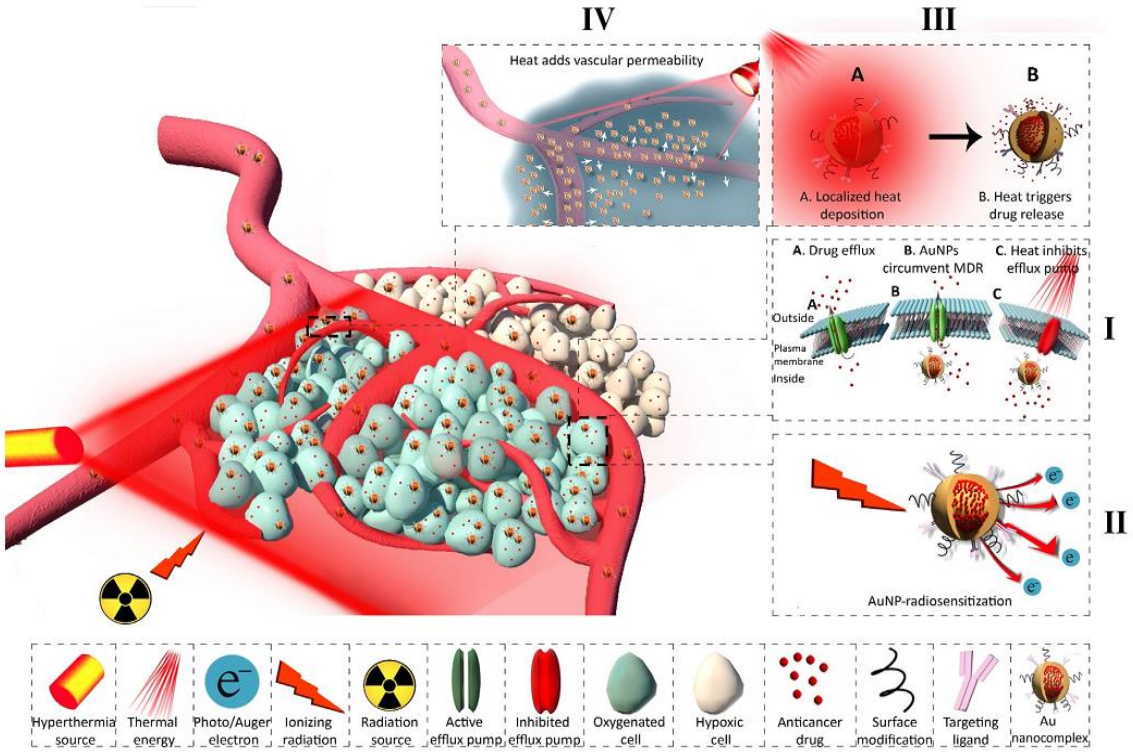


Fig. 1. Heat map showing the biomedical applications of some commonly used inorganic nanostructures. Red color indicates that the respective nanostructure has not been reported to be applicable in a specific therapeutic modality. Bold blue color indicates the extensive use of the respective nanostructure in a specific therapeutic modality.



Scheme 1. Schematic representation depicting the superior benefits of AuNPs-mediated combinatorial cancer therapy.

AuNPs in cancer radiotherapy (RT)

- RT is thought to be a major line of cancer therapy, so that over 50% of cancer patients receive RT with curative or palliative intent.

- RT is based on the use of ionizing radiation which either interacts with DNA as the critical cellular target, directly, or indirectly via inducing radiolysis of water and generating free radicals, eventually resulting in cellular damage.

- However, RT techniques are currently insufficient to destroy radioresistant hypoxic tumors and advanced metastases. As an urgent need, further improvement of RT effectiveness may be realized via incorporation of radiation sensitizers into the tumor.

- AuNPs have been extensively utilized as ideal radiosensitizer agents, offering distinctive merits over other evaluated radiosensitizers (e.g. gadolinium, iodine, platinum), including: (i) high atomic number (Z=79) as the primary need for radiosensitization, (ii) suitable size for passive accumulation within the tumor via EPR, (iii) synthetic versatility to control morphological characteristics, (iv) ability to conjugate with active targeting .ligands and (v) offering diagnostic capabilities for image-guided RT.

- AuNPs were also demonstrated to be able to chemically enhance the radiation-induced reactions through a catalytic function for ROS production.

Table 3
Summary of recent studies on AuNP radiosensitization.

Ref.	Cell line/Tumor model	Au nanocomplex/Size (nm)	RT condition: [Source; Energy; Dose]	Results		
				Comparison index	✗*NPs*	✓*NPs*
Al Zaki et al. [82]	HT1080 human fibrosarcoma	AuNPs-loaded polymeric micelles/75	X-ray; 150 kVp; 6 Gy	Animal survival (days)	38	68
Dou et al. [92]	HeLa cervical tumor	PEG[1]-AuNPs/13.2 nm	X-ray; 6 MV; 6 Gy	TGI[2] (%)	30	80
GAO et al. [83]	HepG2 liver cancer cells	AuNRs[3]-SiO_2-FA[4]/40 × 10	Iodine 125 seeds; 35 KeV; 0.8 mCi	Apoptosis ratio (%)	~21	~33
Li et al. [86]	A431 epidermoid carcinoma cells	PEG-AuNPs/10	Proton; 1.3 MeV; 3 Gy	Enhanced cell death (%)	–	40
Chanda et al. [85]	PC-3 prostate tumor	GA[5]-^{198}AuNP/85	^{198}Au β-emitters; 0.96 MeV; 70 Gy	TGI (%)	–	82
Vilchis-Juàrez et al. [84]	C6 glioma tumor	RGD[6]-^{177}Lu[7]-AuNPs/27	^{177}Lu β- and γ- emitters; 0.497 MeV (β) and 0.208 MeV (γ); 64 Gy	TGI (%)	72	>95
Hainfeld et al. [94]	Tu-2449 glioma tumor	AuNPs/11	X-ray; 100 kVp; 35 Gy	One-year animal survival (%)	18	56
Y.joh et al. [81]	U251 glioblastoma tumor	PEG-AuNPs/23	X-ray; 175 kVp; 20 Gy	Animal survival (days)	14	28
Zhang et al. [80]	U14 cervical tumor	GSH[8]-Au nanoclusters /2.4	Cs-137 γ- emitters; 662 KeV; 5 Gy	TGI (%)	~35	~55
Yang et al. [93]	H1299 non-small lung carcinoma	RGD-GdTc[9]- AuNPs/29	Cs-137 γ- emitters; 662 KeV/10 Gy	TGI (%)	23	77

[1] Poly (ethylene glycol).
[2] Tumor growth inhibition.
[3] Gold nanorods.
[4] Folic acid.
[5] Gum Arabic Glycoprotein.
[6] Peptide based on the cyclic Arg-Gly-Asp.
[7] Lutetium.
[8] Glutathione.
[9] Gadolinium-Technetium.

- AuNPs in cancer hyperthermia
  - Photothermal therapy (PTT)
  - Radiofrequency (RF) hyperthermia
  - Ultrasound hyperthermia

- Cancer hyperthermia refers to the strategy of elevating temperature of the tumor which can be either implemented alone to induce direct cell killing if the temperature is high enough (>45 C), termed as thermoablation, or as an adjuvant therapy to make cancer cells more sensitive to other therapeutic modalities in smaller temperature rises (40–45 C).

- Until now, many clinical experiments regarding the association of hyperthermia and chemo-/radio-therapy have reported improved local tumor control and overall survival in patients suffering from cancer with various origins, such as bladder, rectum, breast, brain, head and neck.

- The major technical challenge facing the use of hyperthermia in practice is to deliver sufficient heat, selectively and homogenously, within the tumors particularly for deep-seated ones. For this purpose, various energy sources are currently employed to heat up the tumor including microwaves, RF .waves, laser and ultrasound.

- Conventional hyperthermia methods are unable to create a discrimination between the heating of tumor and its surrounding healthy tissues. As a result, they are often associated with adverse side effects raised from unwanted heating of normal tissues.

- In nanotechnology-mediated hyperthermia, however, nanoparticles as the primary sources of heat are embedded within the target and may reverse the direction of heat loss (inside-out hyperthermia). Due to their elegant thermophysical properties, AuNPs could potentially be responsive to electromagnetic (EM) waves at different frequencies.

Photothermal therapy of tumor-burdened mice

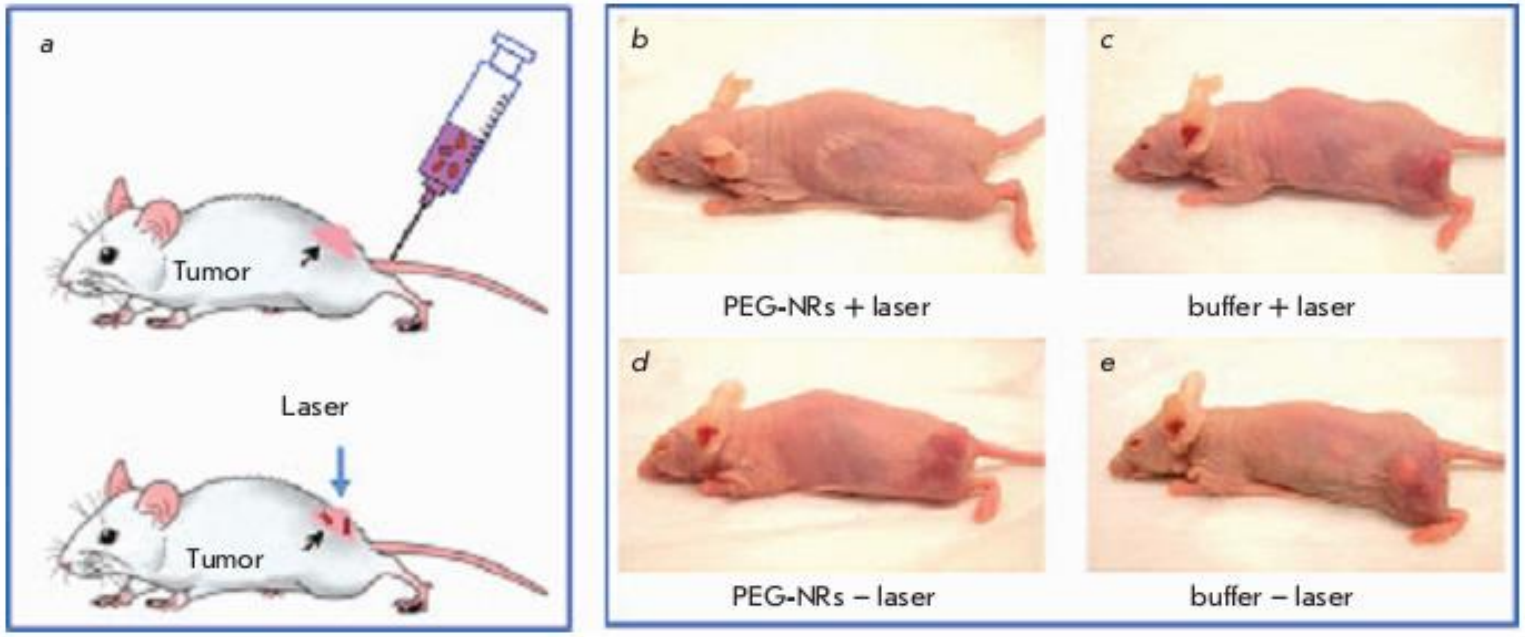


Fig. 8. Scheme (left) and photothermal therapy of tumor-burdened mice (2-3 weeks after injection of MDA-MB-435 human cancer cells into opposite flanks). Laser irradiation (a, b, 810 nm, 2 Wt/cm^2, 5 min) were performed 72 h after injection of PEG-coated gold nanorods (NR) (a, c, 20 mg Au/kg) or saline buffer (b, d). It can be seen that the irradiation without particles (control b), as well as the injection of nanorods or saline without irradiation (controls c and d), had no destructive effect, whereas the nanoparticle and laser treatment completely destroyed tumor. Adapted from Ref. [145] by permission of the Publisher.

Table 4
Summary of recent studies on the use of AuNPs in cancer hyperthermia.

Ref.	Cell line/Tumor model	Au nanocomplex/Size (nm)	HT[1] condition: Source [Parameters]	Results		
				Comparison index	✗*NPs*	✓*NPs*
Liu et al. [147]	MGC803 gastric tumor	AuNRs-SiO_2-CXCR4/86 × 28	Laser [808 nm; 1.5 W/cm^2; 3 min]	TGI[2] (%), T_{max}	0, 38.5 °C	>95, 44.8 °C
Ayala-Orozco et al. [148]	MDA-MB-231LM2 breast tumor	Thiol-PEG[3]-multilayer nanoshells Au-SiO_2-Au /44	Laser [808 nm; 3 W/cm^2; 5 min]	Animal survival (days), T_{max}	7.2, 45.3 °C	15.8, 57.9 °C
Hu et al. [136]	HeLa cervical tumor	FA[4]-PEG-Fe_3O_4-Au core-shell NSs[5]/224	Laser [808 nm; 1 W/cm^2; 5 min]	TGI and animal survival (%), ΔT, η[6]	~0, 5 °C	100, 30.8 °C, 88.9%
Wu et al. [149]	A549 lung tumor	Tube-like Au-attapulgite/ 250–500 × 30	Laser [808 nm; 0.5 W/cm^2; 15 min]	TGI (%), T_{max} , η	0, 34 °C	90, 50 °C, 25.6%
Glazer et al. [137]	Panc-1 pancreas tumor	Cetuximab-AuNPs/10	RF [13.56 MHz; 600 W; 10 min]	TGI (%)	0	~85
Kruse et al. [140]	PC-3 prostate cancer cells	Citrate-AuNPs/10	RF [13.56 MHz; 100 W; 1 min]	Cell death (%)	~50	~75
Cardinal et al. [142]	HepG2 liver cancer cells	Citrate-AuNPs /13	RF [13.56 MHz; 35 W; 7 min]	Cell death (%)	10	80
Beik et al. [146]	CT26 colon tumor	AuNPs/7	Ultrasound [1 MHz; 2 W; 10 min]	Heating rate (°C/min)	1.12	1.54
Beik et al. [150]	CT26 colon tumor	AuNPs/33	Ultrasound [1 MHz; 2 W; 10 min]	TGI (%)	79%	100

[1] Hyperthermia.
[2] Tumor growth inhibition.
[3] Polyethylene glycol.
[4] Folic acid.
[5] Nanostars.
[6] Photothermal conversion efficiency.


Thanks for
attention