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Gold Nanoparticles in Photothermal Cancer Therapy: Current Trends and Outlook

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Abstract

Gold is a multifunctional material that has been utilized in medicinal applications for centuries because it has been recognized for its bacteriostatic, anticorrosive, and antioxidative properties. Modern medicine makes routine, conventional use of gold and has even developed more advanced applications by taking advantage of its ability to be manufactured at the nanoscale and functionalized because of the presence of thiol and amine groups, allowing for the conjugation of various functional groups such as targeted antibodies or drug products. It has been shown that colloidal gold exhibits localized plasmon surface resonance (LPSR), meaning that gold nanoparticles can absorb light at specific wavelengths, resulting in photoacoustic and photothermal properties, making them potentially useful for hyperthermic cancer treatments and medical imaging applications. Modifying gold nanoparticle shape and size can change their LPSR photochemical activities, thereby also altering their photothermal and photoacoustic properties, allowing for the utilization of different wavelengths of light, such as light in the near-infrared spectrum. By manufacturing gold in a nanoscale format, it is possible to passively distribute the material through the body, where it can localize in tumors (which are characterized by leaky blood vessels) and be safely excreted through the urinary system. In this paper, we give a quick review of the structure, applications, recent advancements, and potential future directions for the utilization of gold nanoparticles in cancer therapeutics.

Keywords: Hyperthermia, Photothermal therapy, Regional hyperthermia, Nanoparticle, Gold nanoparticle

Introduction

Plasmonic photothermal therapy (PPTT) is a fast-growing and promising biomedical technology-based therapeutics for cancer management. It shows antitumor capability via local hyperthermia through the localized photothermal effect. The overheating process occurs on the surface plasma of plasmonic agents. When the plasmonic photothermal agent (PTA) is irradiated with absorbable light, the surface plasmons of the agent resonate with the light, electromagnetic waves and

thereby generating active hot electrons [1-4]. The non-radiative decay of these active electrons transforms kinetic energy into heat, which leads to local overheating [5-10]. Compared to traditional cancer treatments, PPTT has a few unique advantages: (1) Typical PTA used for PPTT show potential to bioconjugate with various antibodies, which render them to more accurately and specifically target and kill cancer cells [6-14]. Because hyperthermia only occurs locally where the PTA sets, the localized reaction minimizes the damage to adjacent normal cells [15-18]. (2) It has minimal invasiveness [19-21]. PPTT can be regarded as a gentle treatment without the need for open surgery like tumor resection. This therapy only needs to expose the affected area of the patient to specific light irradiation. (3) PPTT does not lead to drug resistance or chemoresistance [22-25]. PPTT does not need to use any toxic chemical drugs to induce cell death in tumor tissues but only needs to generate a large amount of heat to induce cell apoptosis in malignant tissue [26-30]. Therefore, PPTT has fewer side effects than traditional therapies. Recently, using noble metal nanoparticles as the PTA have received much attention because of their

special characteristics, especially the ultra-small size (~5 - 200 nm) and the unique plasmonic characteristics [31-35]. With contribution from the enhanced permeability and retention (EPR) effect of tumor tissues, the small diameter NPs are ideal to accumulate in the tumor region [36-40]. Among noble metal nanoparticles, the biocompatible gold nanoparticles (AuNPs) have been extensively studied on their capability of producing hot electrons through the localized surface plasmon resonance effect (LSPR) [41-44]. Specifically, when the absorbable incident light impinges on the outer surface of AuNPs, the surface plasmon wave resonates with the electromagnetic wave of the incident light, and the plasma decays into excited electrons via Landau damping and are captured on the surface of AuNPs [45-50]. The non-radiative attenuation of these energetic electrons leads to overheating of the particles and their local environment [51-55]. In addition to the strong LSPR effect, the tunable light absorbance peak is another advantage of AuNPs. By adjusting morphologies, the surface plasma of AuNPs can resonate with Near-Infrared (NIR) light and contribute to the photothermal effect [51-55]. NIR light is ideal for PPTT because it has the best penetrating ability to human skin without damaging the skin and other tissues within a certain power range [56-59]. Results from various calculations have shown that the range of small superparamagnetic particles to large ferromagnetic particles is capable of achieving the maximum total attractive scattering (SLP) (about up to $1W/g^{-1}$) [41-44]. However, hyperthermia studies give greater weight to small superparamagnetic particles due to their much better colloidal soundness [45-47]. Among the most prominent critical perspectives on human civilization is that of gold [48-50]. In prehistoric human cultures, gold was worn by the living as well as the dead as a symbol of wealth and status [51-53]. Gold has been a solid and widely used tool for monetary exchanges and storages from the very beginning of trading [54-57]. As a result of this hunger and confidence in "transmuting anything into gold" [58-62], speculative chemistry emerged as the precursor to modern chemistry. The non-bulk form of gold has already been a part of humanity from the time of relics, very unconsciously [63-65]. Roman cage cups, or diatreme, were decorated and painted with reddish or green colors made of colloidal gold that was scattered in pottery or glass [66-69]. One particularly striking example may be the Lycurgus glass, which dates back to the fourth century A.D. and is composed of glass that is currently held at London's British Historical Museum and is infected with nanogold [70-73]. Despite its long history of use as an opiate and decorative element, the existence of colloidal gold was only intermittently investigated until 1676, when Johann Kunckels, a German scientist, discovered non-bulk gold in a tiny form that was invisible to the human eye. Michael Faraday was an early trailblazer in the major systematic synthesis of gold nanoparticles using decreasing operators based on phosphorus [74-77]. He has received a lot of praise for his extensive and "to begin with" experimental discussion of size-dependent optical characteristics and how they behave when colloidal gold coagulates [46,78-82]. A rapid increase in interest in colloidal gold occurred when electron microscopes became widely available, allowing for direct observation of the nanoparticles [83-87]. Extensive efforts have been undertaken to create and enhance a diverse spectrum of gold Nanoparticles with different sizes, shapes, chemistry, and applications during the last 20 years [88-92]. This paved the path for the use of gold nanoparticles in heterogeneous catalysis, bio-imaging, pharmaceuticals, optics, expository sciences, detection, and other fields [93-96]. With gold nanoparticles finding widespread use in many scientific and technological fields, the need to establish reliable supply chains for these products is growing in significance [46,97-100]. Analyzing the functionalized nanoparticles by encasing them in a cancer cell film revealed that the approaching atom closely resembles the source cancer cells in terms of its antigenic exterior [101-104]. The establishment of an antitumor resistance response was facilitated by these nanoparticles, which enabled the successful transfer of immunological adjuvants and tumor antigens linked with cell membranes to cancer cells [105-108]. There is great promise for theragnostic uses of mesoporous silica nanoparticles. Their fundamental *in vivo* reasonability and extensive cluster of interests make them promising candidates for the treatment of a variety of scourge-inducing diseases in preclinical models [109-113]. oral cancer is difficult to cure and has a dismal survival rate. Evidence suggests that nanoparticle GST prevention has

promise in reversing pingyangmycin and carboplatin medication resistance in oral cancer, hence improving treatment outcomes [114-118]. An undeniable concern with Nanoparticle use is the potential for oxidative stress, which has the potential to cause fatal outcomes [119,120]. It is crucial to organize and explore the subsequent works in order to understand the big picture, as there are many inclinations to use functionalized nanoparticles as cancer theragnostic, and varied considerations have been carried out and are in progress. We might discover long-term job ideas from the existing obligations' totally unique viewpoints [121-125]. Recent studies have shown that photothermal (PTT) and photodynamic (PDT) treatments that respond to near-infrared (NIR) wavelength lasers through the combination of multifunctional plasmon nanoparticles and fluorescent photodynamic agents can achieve a synergistic effect for tumor therapy. Most photosensitizers (PS) are hydrophobic and they require a delivery system to accomplish their tumor therapeutic effects. Much effort has been devoted to the development of dual PTT and PDT therapeutics consisting of a combination of several types of gold nanoparticles and photosensitizers to eradicate tumors. Nonetheless, additional research is needed to improve treatment protocols by regulating optical delivery, power density, and irradiation dose to establish clinical feasibility [126-129]. In this paper, the structure, applications, recent advancements, and potential future directions for the utilization of gold nanoparticles in cancer therapeutics and deals with the types of magnetic nanoparticles, the various functional materials and the techniques for their preparation. An analysis of the literature data on the influence of various physical factors and technological variables on the therapeutic potential of the constructed materials, as well as some approaches to improve their effectiveness, has been performed.

Light absorption in gold nanostructures/S P R

The metal conduction electrons begin to jiggle collectively about their harmony inside the electromagnetic field radiation registry of a metal molecule in response to the recurrence of approaching light [101-105]. Depending on the form, measurement, and composition of the surface chemistry of the metal particle, this mass wavering of conducting electrons is known as surface Plasmon [106-108]. Actually, this tremor triggers the separation of charges in the ionic metal core and the free electrons, and when the coulomb constrain is restored, the electrons move forward and backward at the surface of the particle. In the simplest form, this results in bipolar swaying in circular nanoparticles [109-113]. In **Figure 1**, the schematic of the bipolar electron swaying is shown. Surface Plasmon resonance is the result of the reverberation of conducting electrons and falling electromagnetic radiation; it leads to the solid absorption of light in the visible region and, ultimately, to the formation of colloidal arrangements of metal nanoparticles [114-116]. The traditional defense of this problem has been provided by the May hypothesis, which uses Maxwell conditions for spherical metal particles [130-134].

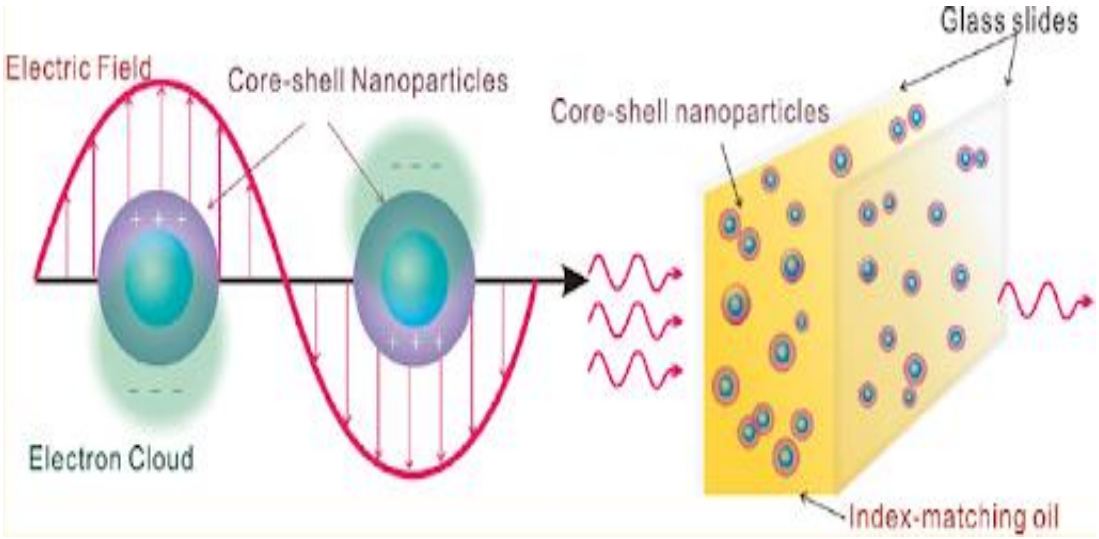

Figure 1 Illustration of electric field-induced Plasmon oscillations in a metal particle and electron cloud displacement with respect to a nucleus [1].

Absorption and scattering of surface plasmon resonance

When electromagnetic waves travel through matter, they undergo 2 processes that lead to their energy dissipating—Total Light Extinction [117-120]. The dissipation of photon energy due to inelastic processes is the first mechanism, light absorption [121-124]. The second process, light dispersion, occurs when photon energy causes electron oscillations in materials; as a result, photons are either scattered light, whose frequency is changed through Raman scattering, or photons are emitted at the same rate as the incident light, a phenomenon known as Rayleigh dispersion [125-129]. Here, the frequency shift is related to the molecular motion caused by the energy difference inside the matter [40,135-140].

The entire Mie principle [41,141-143] is typically used to test the surface Plasmon absorption efficiency; this involves scattering and total extinction [42,144-147]—electromagnetic oscillations with higher orders are more relevant for nanoparticles larger than 20 nm, and all multiple oscillations represent light absorption and scattering. In addition, with a 20 nm Au NP, almost all absorption leads to full extinction [43-44] (**Figure 2(A)**). **Figure 2(B)** shows that the scattering mechanism becomes more apparent as the size increases to 40 nm. Absorption and dispersion both lead to extinction to a similar degree when the scale is raised to 80 nm (**Figure 2(C)**). In addition, the scattering to absorption ratio improves dramatically with increasing particle size, according to the quantitative connection (**Figure 2(D)**). In practice, this fact will dictate the primary biological uses for gold nanoparticles [148-150].

Because light is essentially absorbed with bigger nanoparticles, they are ideal for imaging. Because of this, they may be readily converted into heat that is used for tissue and cell grading. Secondly, photo thermal treatment works best with smaller nanoparticles because they can more readily turn light into heat, which breaks down cells and tissues [151-153].

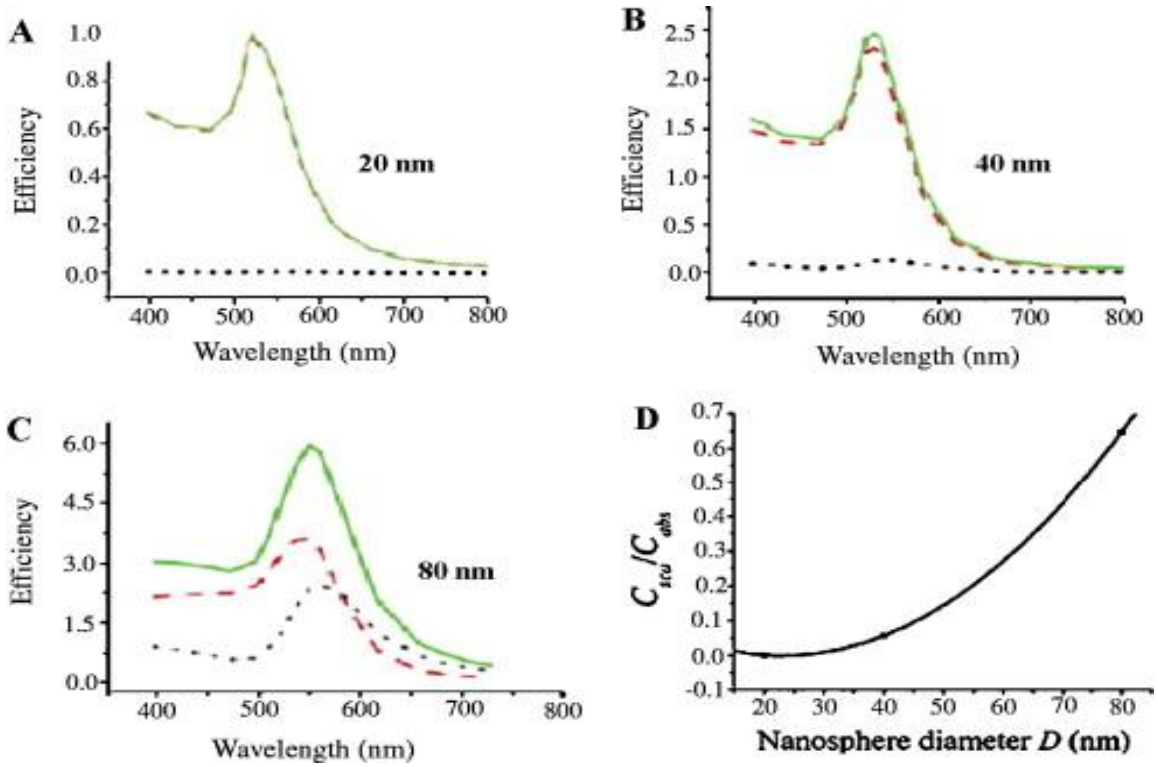

Figure 2 Changing the molecule estimate allows one to tune the relative commitment of surface plasmon assimilation and scrambling. The computed surface plasmon retention, diffusion, and summation termination efficiency of 20, 40, and 80 nm gold nanoparticles, respectively. (D) How the width of gold nanoparticles affects the ratio of diffusing to assimilation cross-sections. Increased commitment from Mie diffusion is caused by increment molecule sizes. The whole Mie hypothesis is used to do the computations [139-140].

Light absorption

Nanotechnology has emerged as a promising approach to enhancing the viability of radiotherapy, offering many unique features that are appropriate for use in cancer [151-153]. Because of their high X-ray absorption coefficient and their ease of engineered handling, which allows for nitty-gritty control over the particle's physicochemical features, gold nanoparticles have garnered the most attention from analysts among the various nano-platforms investigated for radiotherapy applications [154-158]. Colloidal or clustered particles with a nanoparticle's gold core and a surface coating, with diameters ranging from a few to several hundred nanometers, are essentially what are known as nanoparticles gold [159-162]. Their designed mobility, which necessitates altering the features of molecule shape, measure, and surface, is one of the reasons why nanoparticles gold are attractive (**Figure 3**). A fundamental method to incorporate receptive utilitarian bunches to tag, target, and conjugate helpful specialists (e.g., imaging tests, drugs, radionuclides) would be to take advantage of nanoparticles made of gold, which can bind thiols and amines, as well as gold's exceptional optical and electrical properties [163-166]. Several biomedical applications have made use of nanoparticles of gold, including; a) imaging (e.g., photoacoustic imaging, surface improved Raman scrambling, and computed tomography); b) dissemination (e.g., qualities, drugs, and small-interfering RNAs); c) treatment (e.g., photothermal treatment and radio sensitization); and d) integration (e.g., natural and chemical detection into symptomatic stages) (**Figure 4**). The field of AuNP radio sensitization has advanced exponentially since 2004 when Hainfeld *et al.* put out the first logical show of the upgrade consequences of AuNPs radiation measures *in vivo.* In this study, mice were treated with 1.9 nm nanoparticles of gold and 30 Gy of radiation (250 kVp X-rays). The results showed an emotional improvement in one-year survival, going from 20 % with X-rays to 50 % with 1.35 g Au/kg of nanoparticles, and an 86 % increase with the next dose of nanoparticles (2.7 g Au/kg). Following this line of

inquiry, a plethora of studies have shown that nanoparticles offer great promise for effective cellular sensitization to kilovoltage (kV) and megavoltage (MV) radiation both *in vitro* (**Table 1**) and *in vivo* (**Table 2**). Additional types of radio sensitization have recently been developed, illuminating the components with the most promise for radio sensitization of nanoparticles made of gold [44-52,158-160]. These types of sensitizations go beyond the physical upgrading effects that have previously been seen.

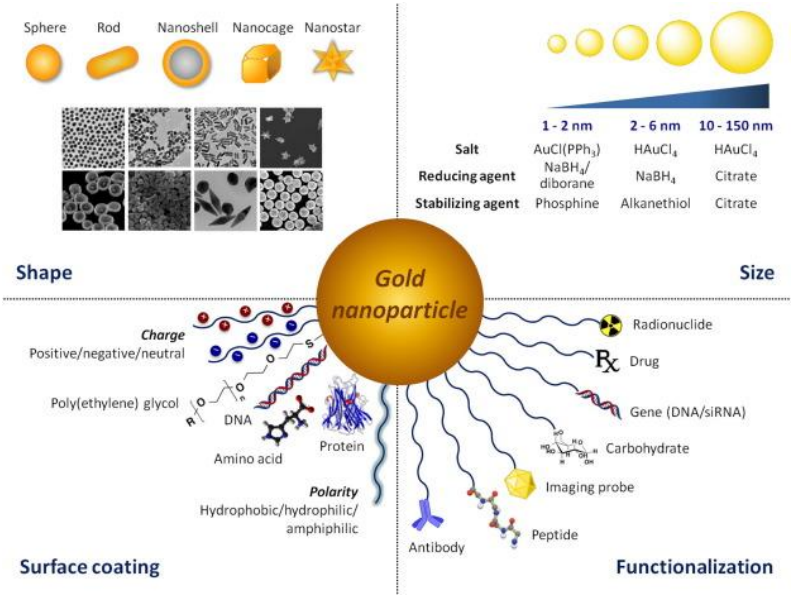

Figure 3 Synthetic gold nanoparticles with remarkable pliability. Nanoparticles made of gold provide a novel platform for controlling the size, shape, and surface area of individual particles, hence enabling the fine-tuning of their characteristics [44].

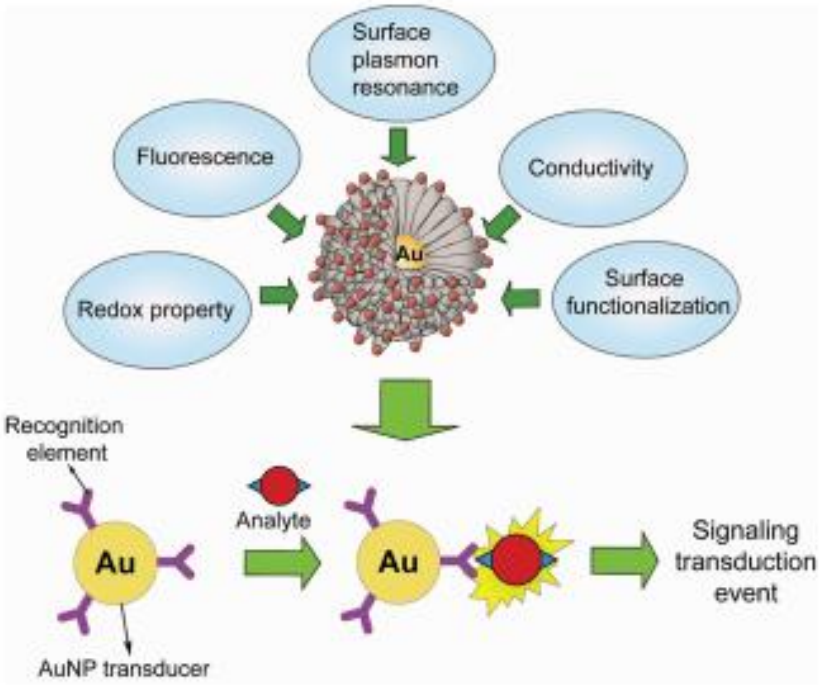

Figure 4 The unique physicochemical, optical, and electrical features of nanoparticles have led to their widespread use in a wide variety of diagnostic, imaging, distribution, and treatment applications, as shown in this article [44,138].

Table 1 Review of *in-vitro* nanoparticles gold Radio sensitization trials [44].

Size	Conc.	Surface	Cell line	Energy	DEF/Effect
-	0.24 μM	(AuroVist™)	Astro	-	0.96
-	-	-	DU-145	-	0.81
-	-	-	L132	-	0.87
-	-	-	MCF-7	-	1.09
-	-	-	MDA-MB-231	-	1.11
-	-	-	PC-3	-	1.02
-	-	-	T98G	-	1.91
30 nm	2.4 mg/mL	PEG	MDA-MB-361	100 kVp	1.6 (targeted)
-	-	HER2 targeted (trastuzumab)	-	-	1.3 (non-targeted)
28 nm	-	-	-	-	-
(18 nm core)	-	-	-	-	-
14	-	-	-	-	1.66
50 nm	-	-	-	220 kVp	1.43
74 nm				660 keV (137-Cs)	1.18
-	-	-	-	6 MVp	1.17
-	(500 μg/mL)	(AuroVist™)	-	-	-
-	(500 μg/mL)	(AuroVist™)	L132	6 MVp	1.29
-	-	-	DU145	15 MV	1.16
-	-	-	-	-	(MDA-MB-231)

Table 2 Review of *in-vitro* nanoparticles gold Radio sensitization trials [44].

Size	Surface	Injection dose (i.v./i.t./i.p.)	Cell model	Energy	Outcome
13 nm	Citrate	200 μL	B16F10	6 MeV e^-	Significant tumor growth
-	-	200 nM AuNPs	-	-	delay; increase in survival
-	-	i.v.	-	-	-
30 nm	PEG	~0.8 mg Au	MDA-MB-361	100 kVp	Tumor growth inhibition
-	HER2 targeted	(4.8 mg/g tumor) i.t	-	11 Gy	(46 % vs. 16 %)
-	(trastuzumab)	-	-	-	-
28 nm	BSA	1.3 mg/mL	U87	160 kVp	Tumor regression
-	(18 nm core)	-	(250 μL)	-	-
-	-	-	i.v.	-	-
1.9 nm	Proprietary thiol	-	-	250 kVp	-
-	(AuroVist™)	2.7 g Au/kg	-	26 Gy	50 % long-term survival (N1 year) at 1.35 g Au/kg

Size	Surface	Injection dose (i.v./i.t./i.p.)	Cell model	Energy	Outcome
-	-	i.v.	-	-	86 % long-term survival (N1 year) at 2.7 g Au/kg
1.9 nm	Proprietary thiol	1.9 g /kg	SCCVII	68 keV	Increase in median survival
-	(AuroVist™)	i.v.	-	42 Gy	(53 vs. 76 days at 68 keV; 31 vs. 49 days at 157 keV)
-	-	-	-	157 keV	-
-	-	-	-	50.6 Gy	-
1.9 nm	Proprietary thiol	4 g Au/kg	Tu-2449	100 kVp	50 % long-term tumor-free
-	(AuroVist™)	i.v.	-	30 Gy	survival (N1 year)
12 nm	PEG	1.25 g Au/kg	U251	175 kVp	Median survival
-	-	i.v.	-	20 Gy	(28 vs. 14 days)
-	nanorods	i.v	-	-	-

Synthesis of gold nanoparticles

Most often, top-down or bottom-up approaches using physical or chemical processes are used to create gold nanoparticles. Using thermal, chemical, or electrochemical partition techniques, bottom-up approaches often deal with gold nucleation placed across smaller structures [161-165]. Primarily, the most often used bottom-up approach is the Turkevich and Brust technique, which relies on reducing metal salts to create spherical, monodisperse gold Nanoparticles with diameters ranging from 10 to 20 nm. It is common practice to use sodium citrate salts as a stabiliser and reducing operator to prevent gold nanoparticles from clumping together during amalgamation [166-171]. Additionally, all amino acids, ascorbic acid, and ultraviolet light have been substituted for citrate as reducing specialists [172-175].

Alternatively, gold Nanoparticles with high solidness may be manufactured in natural arrangements using the Schiffrin-Brust method, which involves exchanging gold from organic to inorganic forms using tetrabutylammonium bromide (TOAB) [176-178]. This technology will be used to generate gold nanoparticles with widths ranging from 2 to 6 nm. The alternative method, known as the Top-down approach, is often used to create nanoscale products from larger macroscale structures. This approach makes use of techniques like lithography. Physical mix methods are often utilized in many different ways; some examples are sonochemical, microwave, and photochemical approaches [179-184]. One newly developed method for mixing gold nanoparticles makes use of natural sunlight (NaValC) and N-cholyl-L-valine, a self-reducing and stabilizing specialist. Light from a 532 nm nanosecond laser, as opposed to an 800 nm femtosecond laser, consistently drives to the arrangement of 40 nm nanoparticles, resulting in a more uniform monodispersing of gold nanoparticles with a 5 nm distance across [5,45,53-55,185-189]. **Figure 5** shows a microfluidic diagram of empty gold nanoparticles going through a series of preparations, each of which has a typical response time. As for the noteworthy nanoparticles, they were supposedly formed at various phases of the process and shown in the insets as TEM representations. The microfluidic chart in **Figure 5** shows the empty gold nanoparticles being guided through a multi-step process with typical response times at each stage. Microscopy images of the nanoparticles made at various stages of the process [45,56-59] are shown in the insets.

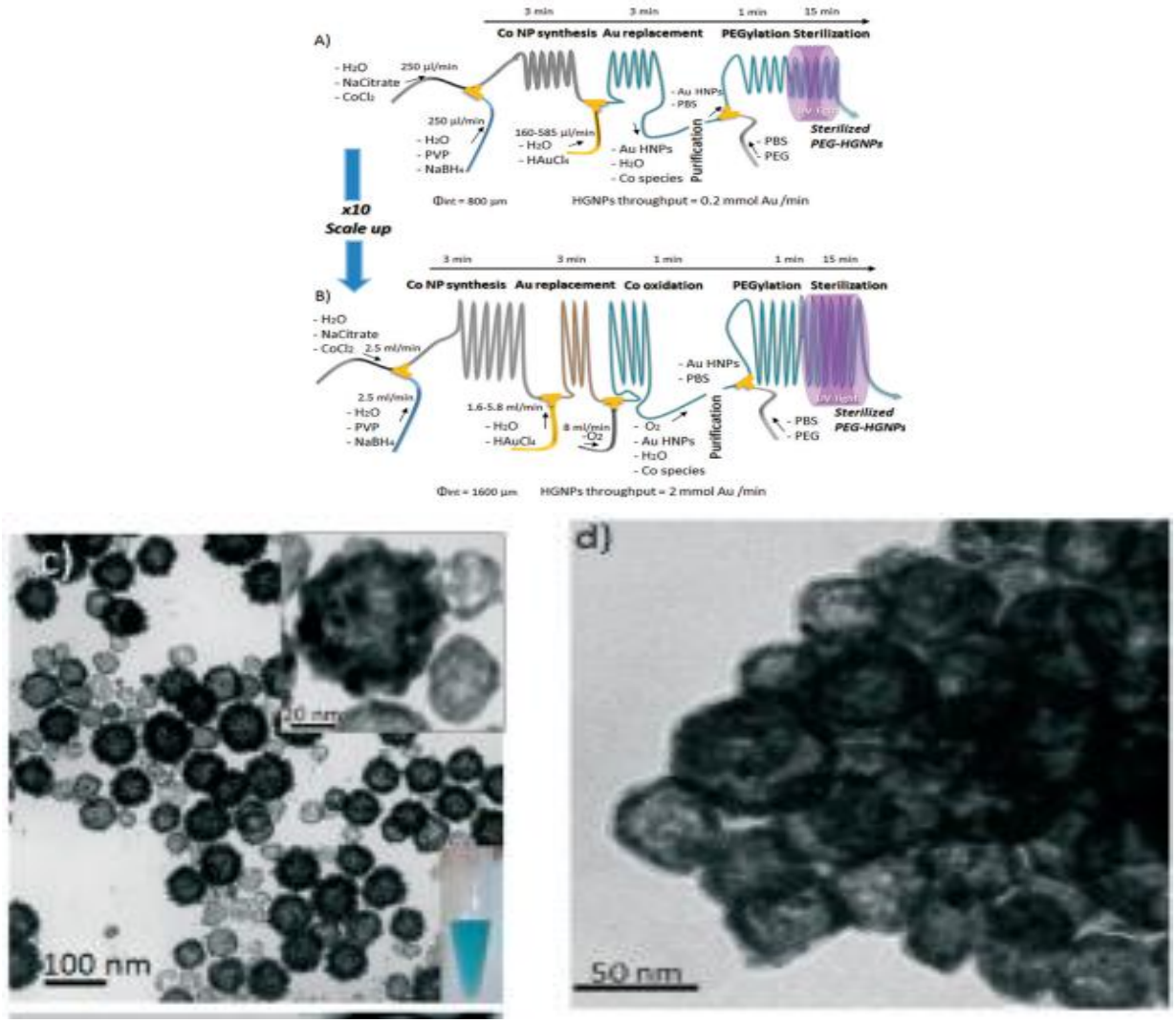

Figure 5 (A) Arrange the experimental setup such that HGNPs are delivered. The dimensions of the reactor are length (913 cm) and inward distance across (800 µm). (B) A 10-fold increase in HGNP throughput achieved by scaling up the microfluidic setup. These are the dimensions of the reactor: length = 3088 cm and internal width = 1600 µm. The materials are shown in transmission electron micrographs at various reactor sites. (C) After 45 min, HGNPs were produced in a clump reactor with a capacity of 480 mL and a concentration of 0.18 mM of Au. d) The microfluidic reactor was used to deliver the as-obtained HGNPs with an S-PEG/Au wt. proportion of 0.005, which is equivalent to 100 times less SH-PEG than the bunch [45].

Surface modification of materiel and methods

Biomolecule detection platforms cannot be created without first modifying their surfaces. The functional groups of biomolecules react with one another and with functional groups on modified surfaces such that they may immobilize. Biomolecules such as DNA, proteins, and carbohydrates are the most crucial when it comes to diagnostic equipment manufacturing [190-193]. In order to include terminal amine and aldehyde groups, DNA oligomers are synthesized. Functional groups such as amino, sulfhydryl, and carboxylic acid are inherent to proteins. Also, as an example, glucosamine has both hydroxyl and amine functional groups, which are considered carbohydrates [194-197]. Based on the set of categories, biomolecule binding is achieved by modifying the surface of the substrate. Biomolecule immobilization has a significant impact on the detection platform's performance. Carbohydrates, including glucosamine, often include hydroxyl and amine functional groups. According to various biomolecule binding classes, the substrate surfaces are changed. When it comes to detection

effectiveness, biomolecule immobilization is king [198-202].

Surface modification with base pairs complementation

Nanomedicine has the potential to revolutionize the treatment of cancer by harnessing the power of biological macromolecules like proteins and nucleic acids. These substances can be used as nanocarriers to transport antitumor drugs, which act on nucleic acids. By attaching these drugs to the surface of gold nanoparticles through engineered double-stranded nucleic acids, the absorption of these drugs into cells can be enhanced. Folic acid (FA) was used as an example to attach to a single-stranded DNA terminal by reacting with its N-hydroxy succinimide ester, which was isolated, with amino-DNA and the complementary strand of DNA conjugated to the surface of gold nanoparticles. Then, after a simple mixture process, the FA-target moiety was simply named on the surface of gold [203-207]. These dimers act either alone or in tandem to transport 1 or 2 anticancer medications that intercalate DNA to many tumor cells. Two tumor cell mRNA targets are 2.5 times more numerous than in normal cells, namely 16 HBE, MRC 5, and A 549 cells (**Figure 6**).

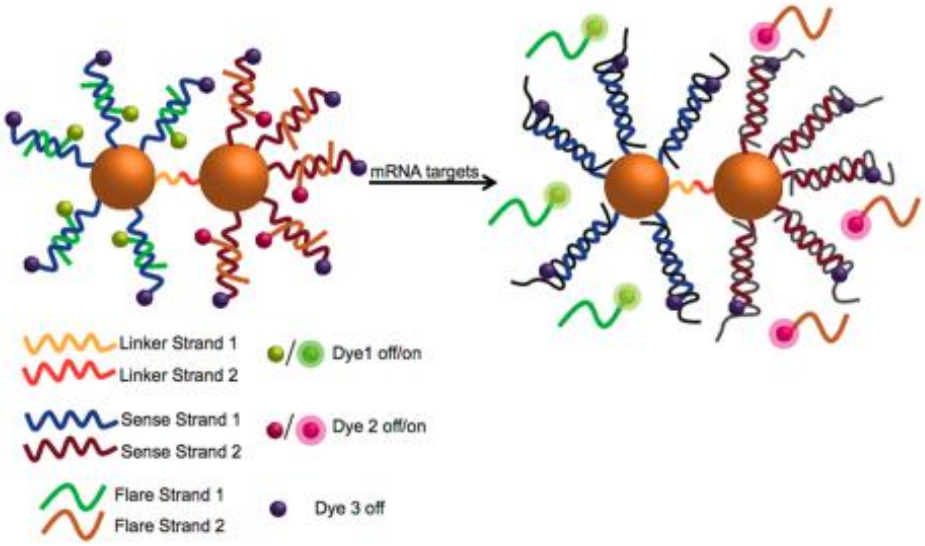

Figure 6 Pharmacological drug release using a multiplexed nanoparticle dimer and a confocal microscopy laser scanning (LSCM) diagram [67].

Surface modification with covalent methods

The term "covalent alteration" refers to the process of attaching gold nanoparticles to one another via chemical bonds. The S-Au covalent bond is the most important interaction that makes the surface chemistry of gold nanoparticles more flexible and smooth [208-211]. The "S-Au covalent bond" is the first stage in the gold Nanoparticles transformation process and is a commonly used denotation. Connecting a short spacer with an ending thiol bunch to the gold surface allows medicinal atoms to be progressively conjugated with chemical responses, and coordinating S-Au contact allows for the tying down of diverse targeting and restorative ligands on the gold surface. **Figure 7** shows the use of antibody-modified P-Si microparticles for the specific capture and localization of HeLa cells [68].

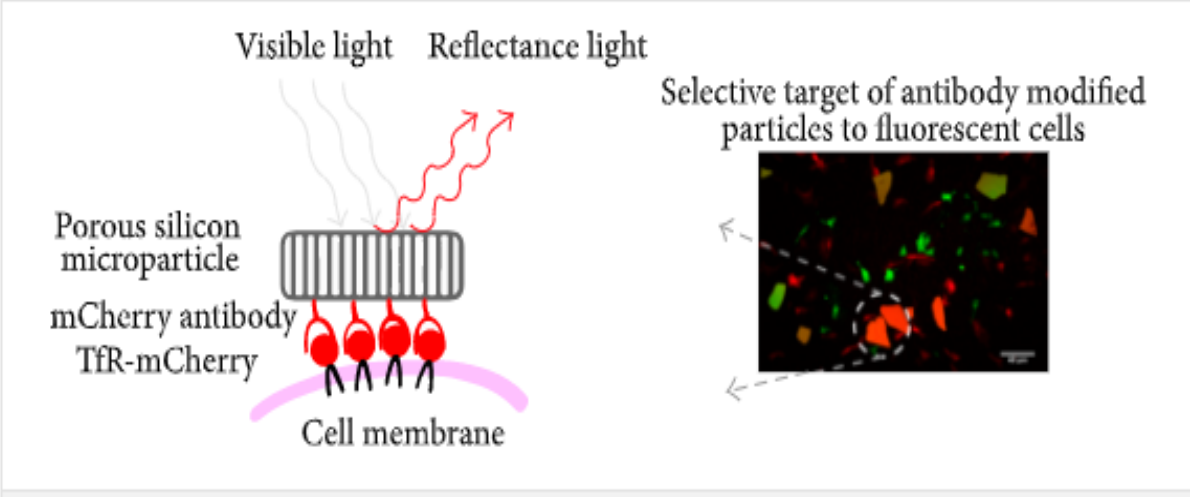

Figure 7 The process of cell detection by covalent attachment of antibodies to P-Si microparticles [68,141].

Surface modification with ligand exchange

Gold nanoparticles are considered an effective and suitable method for functionalizing nanoparticles for use in nanomedicine and biomedicine via the exchange of Ligands for surface modification [212-216]. Reactions involving the displacement of original ligands by biomolecules, medicines, or prodrugs containing thiols are analogous to this mechanism [67]. Nano systems rely on gold nanoparticles for their activities, and in most cases, incoming ligand biomolecules interact with the surface of the inorganic nanoparticles more than leaving ligands [68]. As a result, the therapeutic components of the aptamer, peptide, lipid, and chemical are changed. **Figure 8** A picture of the drug release and detection system utilized in LSCM (Laser Scanning Confocal Microscopy) for mRNA Ruan *et al.* [69] is shown in the schematic diagram. In order to examine the precision of transmission to IL-6R-carrying cells, AIR-3A was tuned to various particle concentrations, and 36, 2 nm, and larger gold nanoparticles were used. Polyethylene Glycol (PEG), particle size, aptamer surface distribution, concentration, incubation period, and temperature all have relative effects on the internalization of the target cell, and the results showed that modifying AIR-3A greatly increased the detection of IL-6R-expressing cells. Just like the modification of poly (ethylene) glycol (PEG), polymers produced by alginate led to colloidal stability and the detection and sequestration of the body's suppressed defense mechanism [217-221]. Conjugating chemical medicines to the surface of gold nanoparticles allows for targeted delivery to tumor sites via selective release. Using a straightforward ligand exchange process, a variety of chemical compounds were attached to the gold surface. These compounds included theobromine (TPN) Ruan *et al.* [69], paclitaxel (PTX) Ruan *et al.* [69], and DOX Ruan *et al.* [69] and DOX Ruan *et al.* [69], which are derivatives of these compounds.

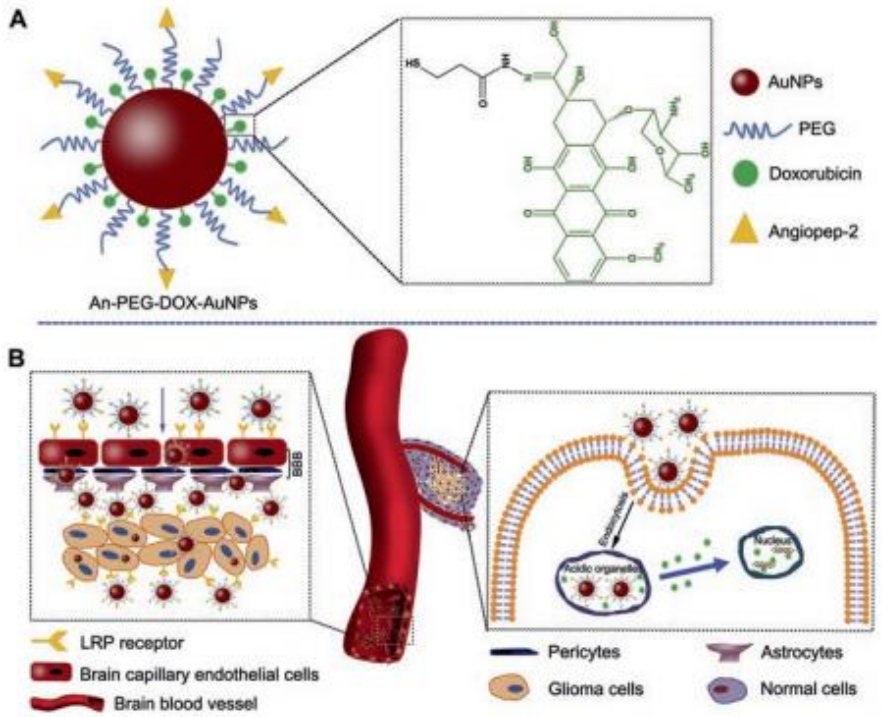

Figure 8 Designed to penetrate the blood-brain barrier and target glioma cells, this schematic depicts the configuration and distribution strategy of An-PEG-DOX-AuNPs [69].

Modification of the surface with chemical reactions

The use of sophisticated synthesis methods was justified by the ligand exchange approach, which altered the surface of the gold. It is necessary to clarify and purify every component. Although it is not cost-effective, this approach ensures that the subject system has the right structure by connecting distinct and more ligands to the surface of gold. Surface modification of gold nanoparticles also made use of modified nanoparticles; this was achieved by first using a short spacer and then, by means of a chemical procedure, by conjugating more ligands onto this spacer. Approximately 70 paclitaxel molecules per nanoparticle make up the hybrid nanoparticles covalently linked organic shell, which accounts for about 67 % of the total mass, as determined by thermogravimetric analysis (TGA) [222-226]. The potential for drug delivery via integrated frameworks with many features is immense, but the development of technology to construct fully functionalized systems has impeded this advancement in nanomedicine. Over a 10-day period, the Pt (II) release for 1non-PEGylated, 5 K-PEGylated, and K-PEGylated conjugates remained the same, when tested at 0.5 Pt (II)/2nm drug loading [227-231]. A lack of technology to construct completely functionalized systems has impeded this advancement in nanomedicine, despite the tremendous potential of integrating several functionalities in a single framework for medication delivery [67]. **Figure 9** shows the results of this disease-specific drug delivery system's modular synthetic technique, which provides an ideal and straightforward picture of Nano carrier topologies [72].

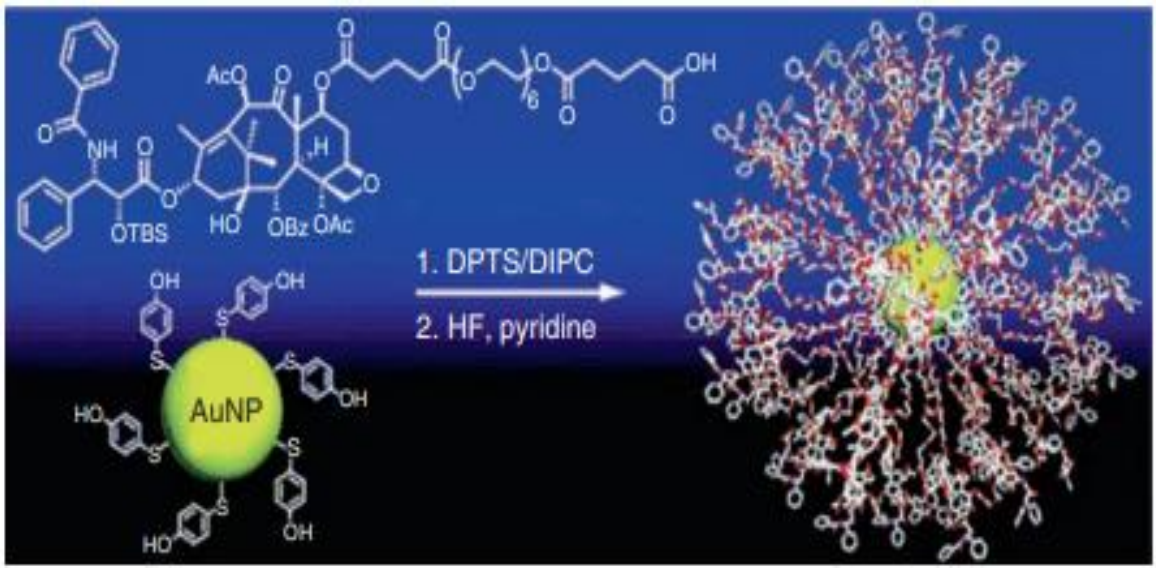

Figure 9 Covalent coupling of paclitaxel schematic [70].

Surface modification with click chemistry

A wonderful, fast, and easy key surface alteration handle, tap chemistry is based on the carbon-heteroatom bond [232-235]. It does not modify the structure of Nanoparticles. A possible lesson in biocompatible small atom reactions used in bio-conjugation and chemical amalgamation, "press" chemistry allows for the joining of intriguing biomolecules to substrates of choice. The development of copper-free tap chemistry has recently received increased attention due to the fact that it improves the bio-safety of *in vivo* press reactions. A cytotoxic chemical, a cancer-cell targeting ligand, and an imaging moiety were conjugated onto a multifunctional gold nanoparticle. Among all surface modifications, azide-alkyne cycloaddition [236-240] was pioneered by B-cells using the glycan-based ligand in conjunction with the CD22 strain of the cell surface receptor. The surface-bound CD22 allowed the nanoparticle to undergo receptor-mediated endocytosis more rapidly than nontargeted nanoparticles. Coating AuNPs with a useful copolymer, CuAAC was created by adjusting polydimethylacrylamide (DMA) with an alkyne monomer. This allowed for the official production of azido-modified particles using Cu(I)-catalyzed azide/alkyne 1,3-dipolar cycloaddition [241-245]. It was possible to realize the azido-modified protein due to the polymeric spine. Connected to the surface of the molecule at that time, the anti-mouse IgG counteracting agent would go on to achieve legendary status in bio detection approaches (**Figure 10**) [75].

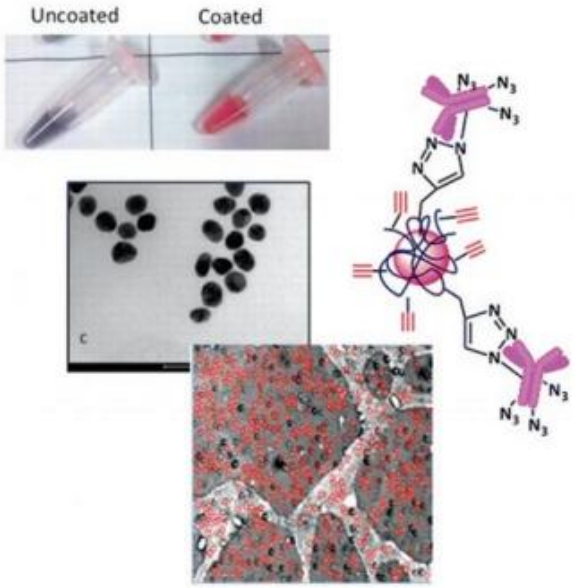

Figure 10 In addition to their picture, transmission electron microscopy (TEM) and interferometric image, the gold nanoparticles were functionally changed with a polymer and derivatized with an antibody polymer that had been treated with azido [75].

Silicon modification

Among the elements in the periodic Table, silicon is one that is seldom found in its pure form. The stable oxidized state is where it occurs. Silicon is a semiconductor that finds widespread usage in electrical equipment. The label-free and real-time detection capabilities of protein electrochemical detection have made it famous. Since controls over temperature and humidity are not necessary for physical adsorption, it is one of the choices for antibody immobilization [246-248]. The shorter duration of immobilization allows for a faster test compared to other techniques. The development of pseudo-3-dimensional surfaces for immobilization is enhanced by the porous shape of silicon, which in turn increases its effectiveness. The porous silicon (P-Si) surface exhibits excellent spot uniformity, little internal fluorescence, poor wetting capability, and reduced non-specificity. Depending on the pore size, P-Si may be classified as microporous (less than 10 nm), mesoporous (10-50 nm), or microporous (more than 50 nm) [249-251]. There have been reports that the microporous silicon surface is ideal for antibody immobilization. Surface modification of silicon nanoparticles is graphically shown in **Figure 11** [76]. Surface modification and Fourier transform infrared spectroscopy analysis of nanoparticle powders were carried out as described in the experimental section. Pure citric acid powder and Si-np and M-Si-np spectra are shown in **Figure 12**. The carbonyl groups' C=O stretch is reflected in 2 separate absorption peaks at 1748 and 1702 cm^{-1} in pure citric acid. As a result of interacting with silicon nanoparticle surfaces, citric acid's carbonyl peaks are converted to silyl esters (-Si-O-C(O)-C-) at 1725 and 1630 cm^{-1}. **Figure 13** shows the results of electrochemical studies that were conducted on both fresh and CA surface modified silicon nanoparticles to assess the quantity of citric acid on the active material's surface. The nitrogen content of both samples was measured after they were vacuum-dried. There is no weight loss of 0.7 % for the M-Si-np at temperatures up to 3500 C, while there is none for the Si-np. When both samples were handled under identical circumstances, the weight loss seen with the M-Si-np might be attributed to a decrease in citric acid. **Figure 14** shows that around 1 monolayer of citric acid is lost in the process of silyl esters production [77-79].

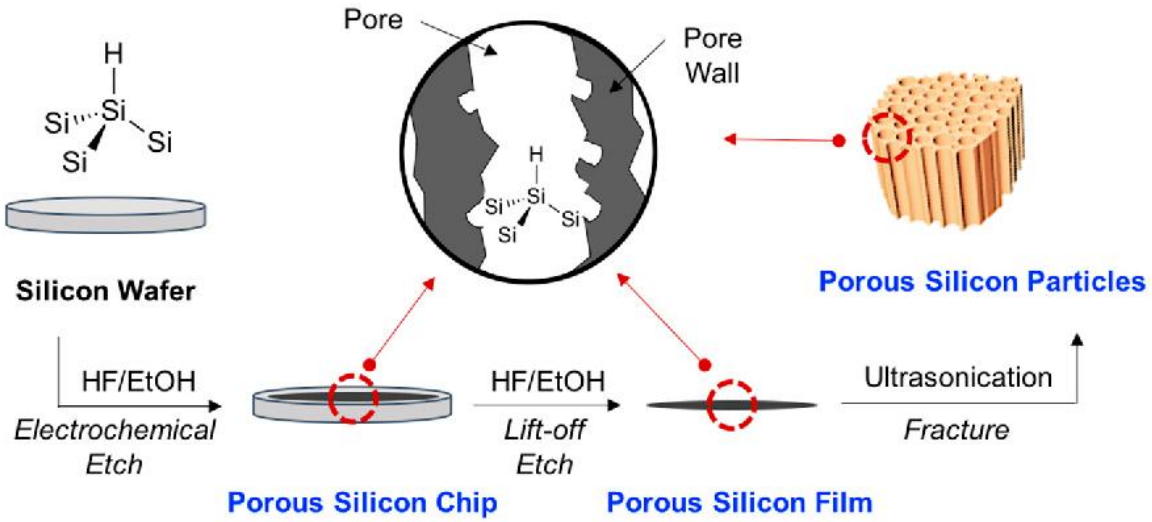

Figure 11 Diagram depicting the process of preparing porous silicon by electrochemical etching and ultrasonication [77].

A porous silicon layer may be created on a silicon wafer's surface by electro-chemical etching and then lifted off the wafer via lift-off etching. It is possible to create micro- and nanoparticles of porous silicon by means of ultrasonic drilling. Silicon hydrogen (SiH) and silicon oxygen (SiOH, SiOSi) provide some protection to the surface of the produced porous silicon [76-79].

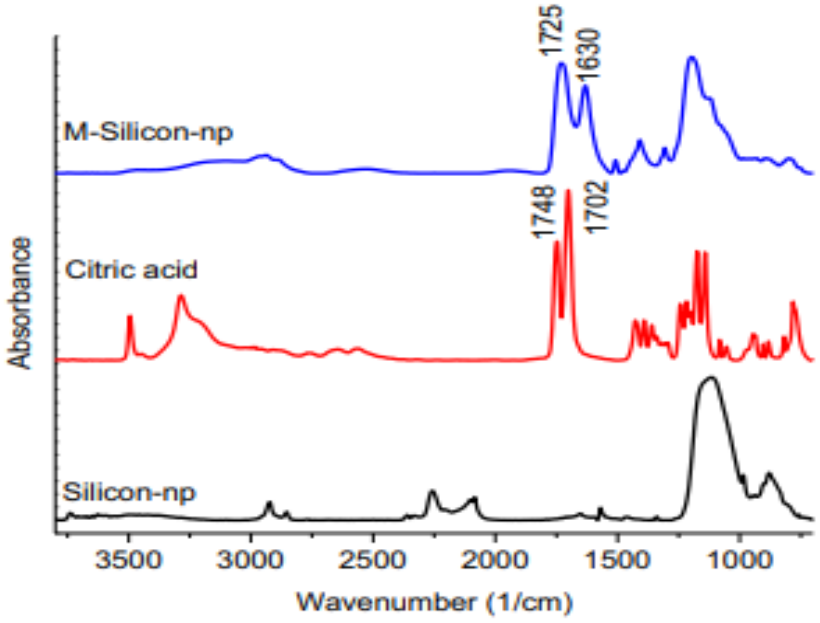

Figure 12 Powder-modified citric acid Silicon nanoparticles (red), CA (blue), and FTIR-Silicon nanoparticles' ATR spectra (black) [77].

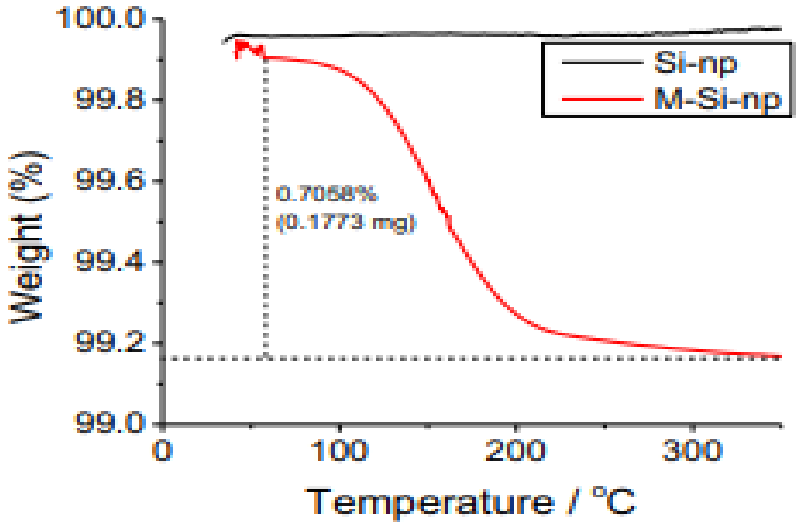

Figure 13 Surface modifications caused by TGA of new SNPS (black) and CA Silicon nanoparticles (red) [77].

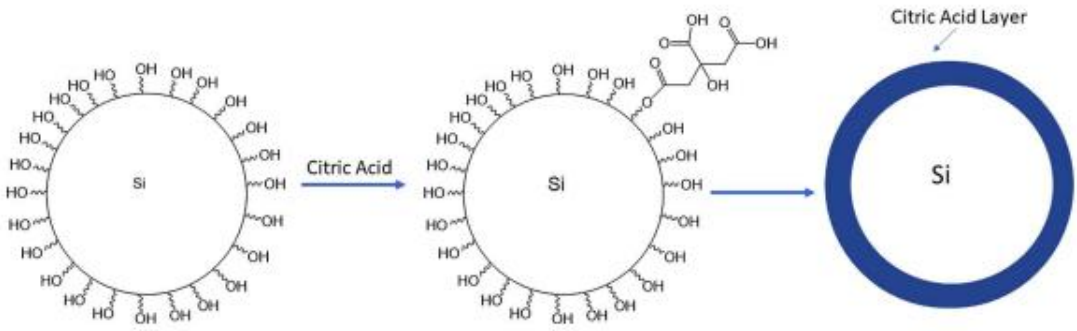

Figure 14 A simplified diagram showing the surface modifications of SNPs [77].

Electrochemical modification

Micro- and nanomorphology, controlled by surface etching and silicon form selection, has a significant role in the physisorption of P-Si biomolecules. According to reports, a significant amount of effort is required to prepare micro- and nanoporous silicon for antibody adsorption.

Lee *et al.* [76] selected and placed a boron silicon wafer in the electrochemical cell with a specific resistivity of about 6 - 8 Ωcm. **Figure 15** shows that a self-supporting layer of P-Si may be created by first developing an anodic oxide and then dissolving it in a 15 % hydrofluoric acid solution using an electropolishing current. This process causes pores to form. After that, the microporous P-Si is diced and placed on a microtiter plate for the capture antibody deposition (cAb) step of the sandwich immunoassay. Various substances and microorganisms may be electrochemically detected using P-Si surfaces, as discussed in several articles [252-256].

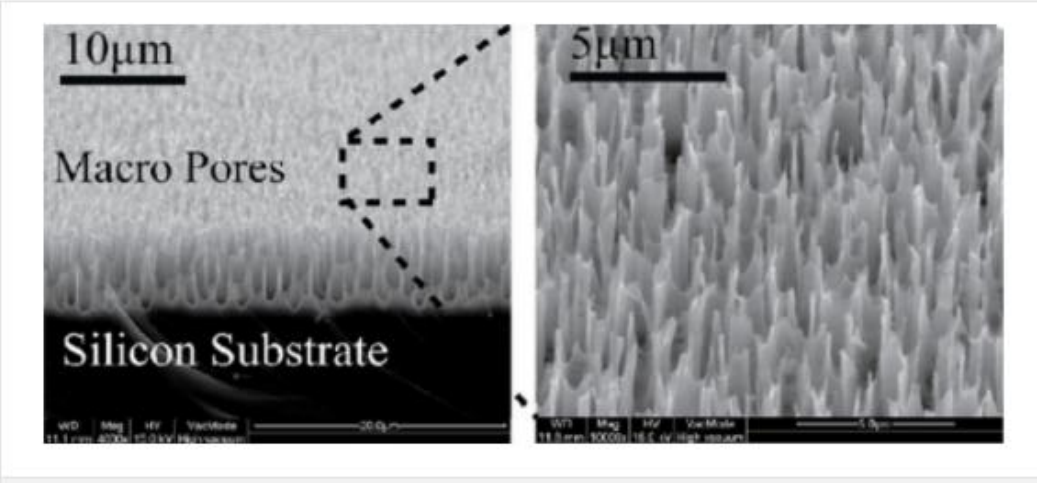

Figure 15 A layer of microporous polycrystalline silicon [80].

Glass (SiO_2) modification

The chemical formula for glass is SiO_2. The oxide layer that forms on silicon is a result of chemical reactions and oxidation. Silicon dioxide is both thermally stable and common in nature because of the quantity of silicon and oxygen bonds. Substrates made of glass are easy to work with, widely accessible, and mechanically stable [257-260]. Glass surfaces are often used for the immobilization of biomolecules with low molecular weights, such as DNA and proteins. As a microarray location, the glass surface is crucial in the diagnostic sector for identifying various pathogenic DNA and biomarker proteins [81]. **Figure 16** shows the chemistry of glass surface change using a PNA probe.

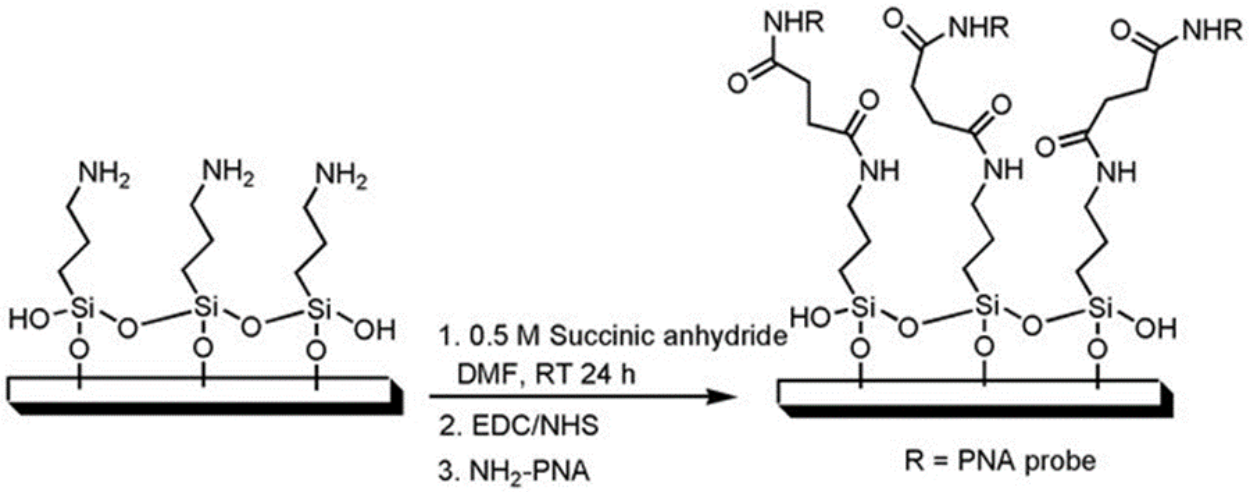

Figure 16 Using a PNA probe to modify the chemistry of glass surfaces [81].

Physisorption based modification

Physical adsorption, often known as physisorption, is one of the most basic techniques for immobilizing biomolecules on glass surfaces. The phosphate backbone of DNA, which is negatively charged, produces an ionic connection with the positively charged surface of the amine-modified glass, as shown in **Figure 17** [82].

Lemeshko *et al.* [82], the positively charged surface is created via aminosilanization of the glass surface by treatment with 3-(aminopropyl) trimethoxysilane (APTMS). The lack of a location for repeatable DNA identification is an unfortunate consequence of DNA immobilization using this method. With the DNA backbone's numerous interactions with the cationic surface and its orientation parallel to the glass surface, its availability for hybridization with

cDNA is therefore minimal. The spontaneous orientation of immobilized DNAs is also responsible for nonspecific hybridization and poor repeatability. The process efficiency is significantly impacted by variations in solution pH and temperature, which vary with the physisorption system [82-87].

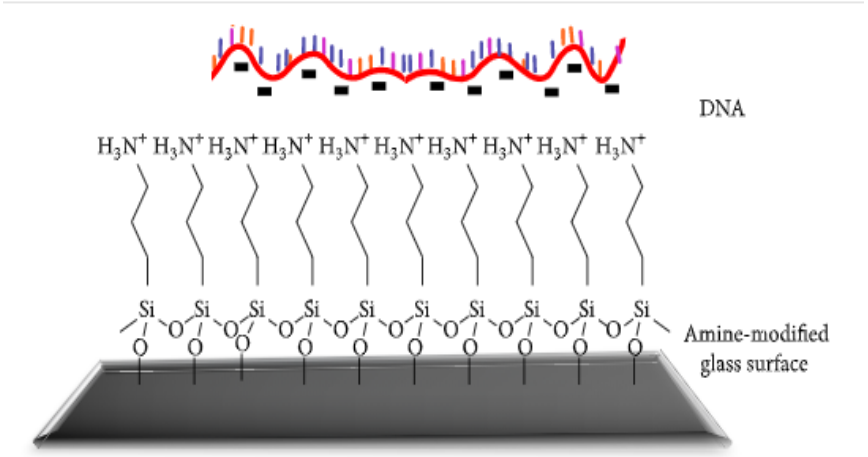

Figure 17 Glass surface modification by amines for DNA physisorption [82].

Gold nanocages

Gold nanocages are created by shaping silver nanostructures into 3-dimensional shapes using a salt of gold chloride. As seen in **Figure 18(a)**, gold nanocages are basically empty structures with a porous, inclined, and robust gold interior. Changing the concentration of gold chloride used determines the most significant adsorption of nanoparticles, which in turn changes the divider thickness of nano cells (**Figure 18(b)**). Both the total and the leading remarkable maintenance wavelengths grow with increasing gold divider removal over [261-264].

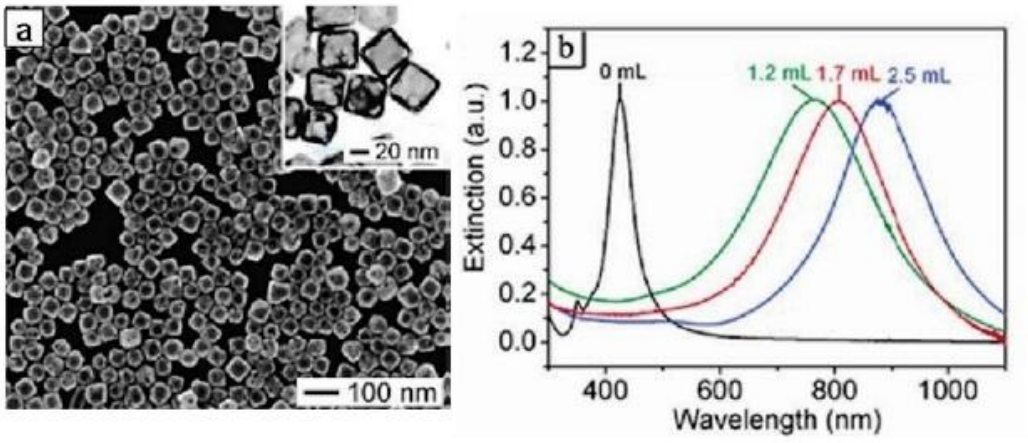

Figure 18 (a) Images captured by scanning electron microscopy of gold nanocages. (b) Optical absorption spectra of gold nanocages made with varying amounts of gold [5].

Future directions: Green synthesis of natural substances embedded with gold nanoparticles

Some benefits, not seen in conventional synthesis techniques, may result from natural processes of material separation and processing from gold nanoparticles. The medicinal features of green synthesis gold nanoparticles, such as antibacterial and anti-cancer capabilities, and the reduction and stabilization of

nanoparticle synthesis agents are enhanced by the use of natural chemicals [265-267]. Due to the reduction in residual chemicals needed for the synthesis of gold nanoparticles, this method is considered the most effective and may aid in the production of gold nanoparticles with little to no side effects. In addition, the green production of gold nanoparticles is mostly focused on bacteria, fungi, and plants (**Table 3**) [88,89].

Table 3 Green chemistry for nanoparticle gold synthesis.

	Source	Size (nm)	Morphology	References
Bacteria	*Bacillus megatherium* D01	1.9 ± 0.8	Spherical	[90]
	Bacillus subtilis 168	5 - 25	Octahedral	[90]
	Escherichia coli DH5α	25 ± 8	Spherical, triangular, and quasi-hexagonal	[90]
	Escherichia coli MC4100	10 - 25	Spherical, triangular, hexagonal, and rod shape	[90]
	Geobacillus sp.	5 - 50	Quasi-hexagonal	[90]
	Lactobacillus strains	20 - 50	Crystalline, hexagonal, triangular, and cluster	[90]
	Plectonema boryanum UTEX 485	10 up to 6 μm	Cubic and octahedral platelet	[90]
	Pseudomonas fluorescens	50 - 70	Spherical	[90]
	Rhodopseudomonas capsulata	10 - 20	Nanoplate and spherical	[90]
Fungi	*Fusarium oxysporum*	8 - 40	Spherical	[91]
	Verticillium sp.	5 - 200 (average 20 ± 8 nm)	Spherical	[92]
Plant	Apiin extracted from henna leaves	7.5 - 65	Quasi-spherical	[93]
	Camellia sinensis (green tea)	40	Spherical, triangular, irregular	[93]
	Coridandrum sativum (coriander)	6.75 - 57.91	Spherical, triangular, truncated triangular, decahedral	[93]
	Cymbopogon flexuosus (lemongrass)	200 - 500	Spherical, triangular	[93]
	Eucalyptus camaldulensis (river red gum)	1.25 - 17.5	Crystalline, spherical	[93]
	Medicago sativa (alfalfa)	2 to 40	Platelet that is irregular, tetrahedral, hexagonal, decahedral, and icosahedral	[93]
	Mentha piperita (peppermint)	150	Spherical	[93]
	Murraya koenigii	20	Spherical, triangular	[93]

Photothermal cancer treatment using spherical gold nanoparticles

Due to its fundamental unity, production in sizes ranging from 1 nm to 100 nm, and most outstanding light maintenance within the 500 - 600 nm range, gold circular nanoparticles have emerged as the most popular and extensively used kind of GNPs. Photothermal treatment, which converts light into heat using gold nanoparticles, is effective against cancer on its own or in combination with other supplementary tactics [266,267], and the primary wavelength of these

structures' maintenance is transmitted to higher wavelengths as the particle degree increases.

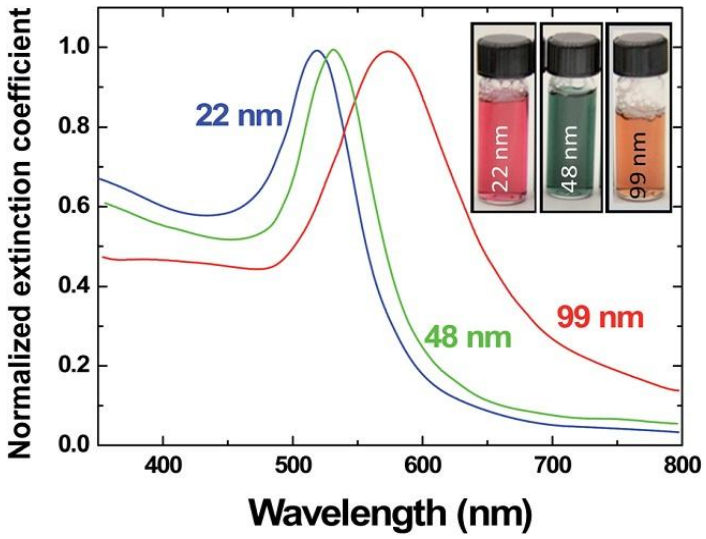

Figure 19 As the size of the gold spherical nanoparticles changes, the maximum absorption wavelength of surface plasmon resonance (SPR) moves to longer wavelengths [5].

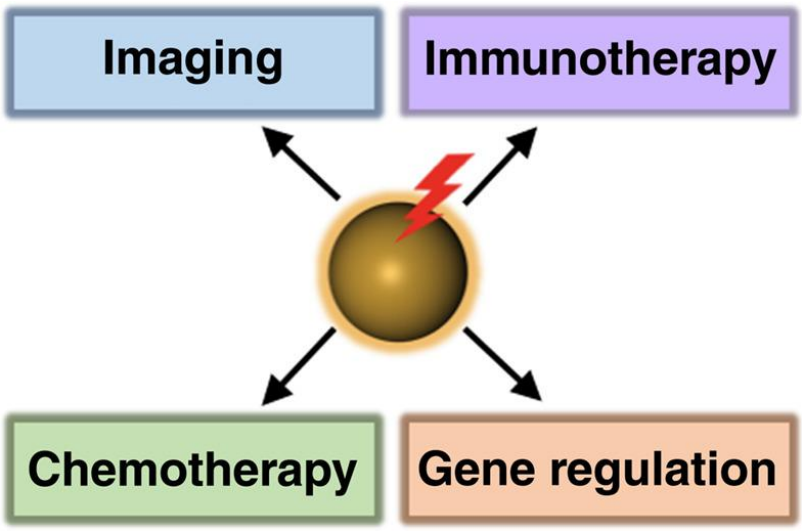

Figure 20 Photothermal therapy gold nanoparticles [5].

Mechanism of photothermal therapy

Most people think that nanoparticle-containing cells may destroy cancer cells by converting the absorbed light into heat in a matter of femtoseconds when exposed to laser radiation. A variety of non-radiative methods allow gold nanostructures to transform light-absorbed heat into heat. Typically, in a few femtoseconds, the process of transforming light into heat starts with electron-electron collisions in phase-excited proton beams. Within about a second, the electron transfers this energy to phonons through an electron-phonon interaction, creating a hot network and raising the temperature by several tens of degrees. No matter the size, shape, or presence of transverse or longitudinal Plasmons in gold nanorods affects the electron-phonon interaction process. The following 3 processes are possible [16-18] depending on the energy of this hot network:

1) Over the course of around 100 picoseconds, the network is cooled by releasing energy into the surrounding environment via phonon-phonon comfort. The environment becomes hotter as a result of this

process. Nanoparticles linked to or aggregated in cancer cells may be killed by this fast energy conversion to heat.

2) If the network's heating rate is much higher than its cooling rate (the rate at which heat is transferred to the environment), then structural changes like melting or fragmentation of gold nanostructures may occur.

In only a few hundred femtoseconds, the network's thermal energy after laser irradiation is sufficient to burn the whole particle.

We need to aim to make process number 1 the dominant process if we want to employ nanostructures to destroy cancer cells. In most cases, this procedure is affected by the laser's type (continuous or pulsed wavelength), as well as the radiation's intensity and duration. Light energy is efficiently converted into heat by gold nanoparticles. Here are 2 key factors that are unique to gold nanoparticles that explain this. Because of 2 factors: First, the strong absorption of irradiation light by gold nanoparticles (SPR) and second, the fact that only a little portion of the absorbed light is actually irradiated (hence the lack of photoluminescence). PDT's fame has endured for decades. Light accelerates the process of cell death in cancer cells compared to nonmalignant tissue once a photosensitizer (PS) accumulates in them. Light of a certain wavelength triggers the activation of PS. When reactive oxygen species (ROS) and oxygen react, a byproduct is superoxide hydrogen gas, or O2-. Oxygen 3O2 and PS establish a connection in cytotoxic singlet O2, which causes oxygen transformation. In **Figure 21**, we can see that O2- and 1O2 are produced by cells dying in 2 ways: Directly, via necrosis and apoptosis, and indirectly, through microvascular disruption and the immunological response to anticancer substances. **Figure 22** shows the 3 steps that cells go through when they die: cellular membrane destruction, denaturation of tumor DNA, and angiogenesis stopping.

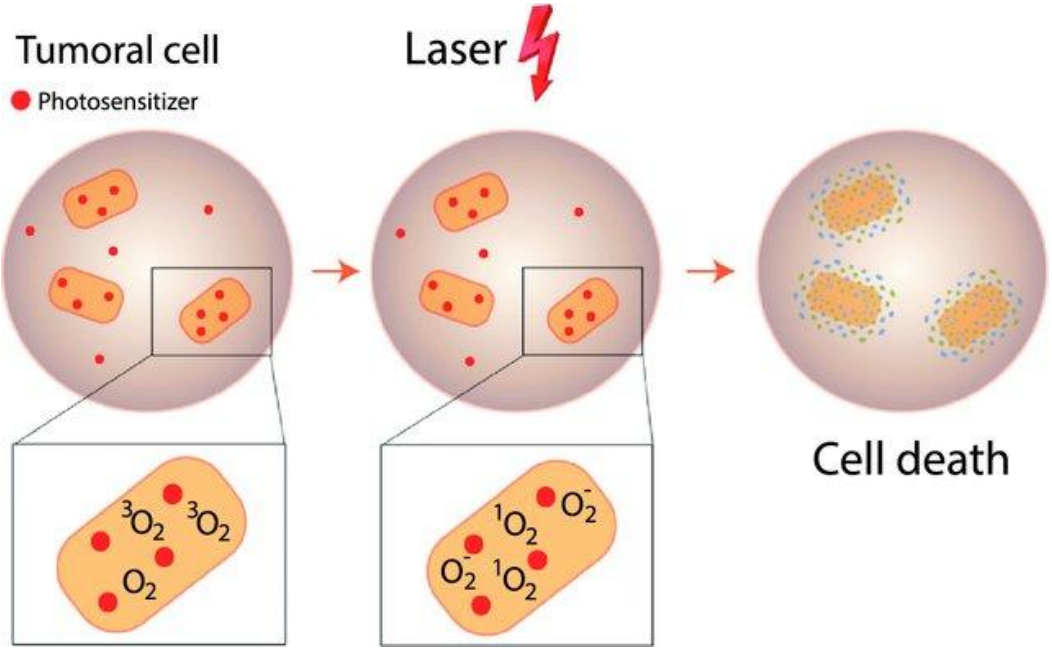

Figure 21 Mechanism photodynamic therapy [5].

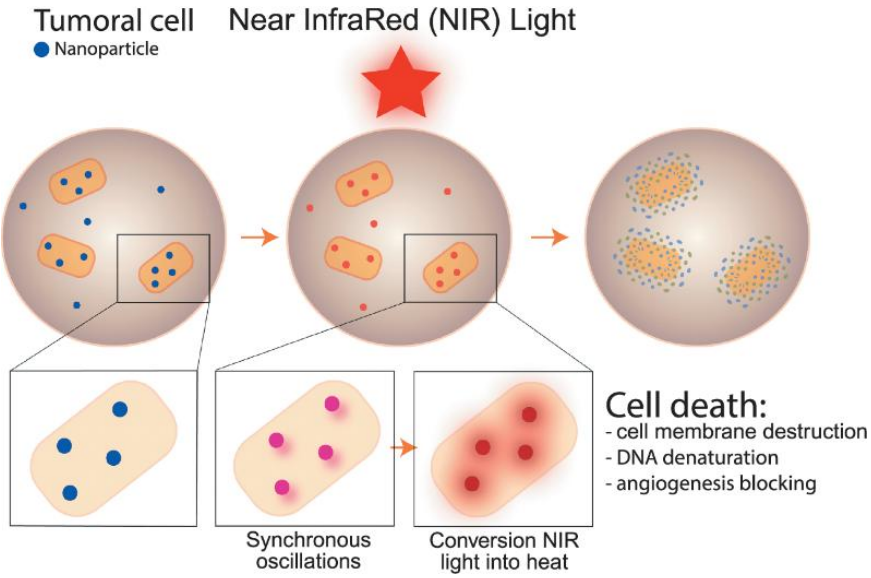

Figure 22 Mechanism photodynamic therapy [5].

Photothermal therapy with gold nanospheres

Gold circular nanoparticles convert virtually all of the light that enters them into heat, and they retain self-evident light a million times more than typical hues. Along with their high biocompatibility, these nanoparticles are very persistent when exposed to light. These features, along with others, make these particles an excellent starting point for developing novel photothermal treatments. It is possible to use both continuous-wave and pulse lasers to perform photothermal therapy on gold circular nanoparticles [18,19]. Because of the SPR absorption of these particles inside the visible region (wavelength about 500 nm), they are only useful for superficial cancers like skin cancers and not practical for deep cancers (since visible light (wavelength 500 nm) can penetrate bodily tissues). This is how it works since it is relevant to light-sensitive, superficial cancers. Although connecting cells that needed nanoparticles but were illuminated with laser survived, the fundamental study that came up with the idea in 2003 included sending 100 pulses of light at 0.5 joules per square centimeter into cancer cells. Using this control, the surface temperature of the nanoparticles in each laser radiation pulse increases to 2000 K, and the transferred heat is exchanged at a scale of up to 15 nm, according to the modeling considerations.

Recent research into the use of nanosecond pulse lasers has shown promise for targeting damage within a range of a few nanometers to several micrometers, depending on the pulse duration and molecular degree. Because of this, removing cancer cells from micrometer tumors was a must. In a separate study conducted by El-Sayed *et al.* [20], researchers found that 40-nanometer gold nanoparticles might be used to combat head and neck malignancies by interacting with the EGFR counteracting administrator. Cancer cells and cells without nanoparticles were seen after 4 min of argon laser illumination at 524 nm and 19 watts per square centimeter [20].

Photothermal therapy with gold nano shells

Due to its low absorption by hemoglobin and tissue water, near-infrared light (NIR) is the preferred method of targeting deep cancers and tumors beneath the skin. Consequently, this light spectrum is essential for the functionality of the nanoparticles. The first in-body and out-of-body investigation in the near-infrared (NIR) spectrum using a gold nano shell took place in 2003. In this work, a continuous wavelength laser was used to target and destroy gold nano shells inside the infrared area of breast cancer cells for a duration of 4 min. MRI revealed a 30-degree rise and tissue damage after tumor injection of nanoparticles and laser irradiation. Coating the nano shells with polyethylene glycol (PEG) and injecting them into an intravenous stream was used in another investigation. Mice showed no signs of reversibility after 90 days of testing. Following this, antibodies and other targeted agents

were applied to this structure, and it was subsequently used [1-5].

Photothermal therapy with gold nanorods

Nano thermal treatment using gold nanorods was carried out *in vitro* by Al-Sayed *et al.* in 2006. In this work, cancer cells from the head and neck were exposed to continuous-wave laser irradiation at 800 nm (the maximal absorption wavelength for nanorod plasma) for 4 min after being linked to anti-EGFR-conjugated gold nanorods. The laser strength utilized to kill cancer cells was 10 w/cm^2, which is far lower than the high power needed to kill healthy cells (20 w/cm^2). This shows that the laser was properly targeted on cancer cells, since cancer cells express more EGFR than healthy cells. Because of their strong absorption in the near-infrared (NIR) region at the same wavelength as nanoshells, using nanorods needs 3 times less laser power than using nanoshells. Recent research has shown that converting linearly polarized light to spherically polarized light greatly boosts light absorption by nanorods, resulting in a fivefold reduction in the threshold for cancer cell death. According to theoretical research, a laser with an intensity of 30 J/cm^2 may transmit heat from nanorods, raising the cell temperature by 10 degrees and leading to cell death by rupturing the cell wall. Compared to when the nanorod reaches the cytoplasm, the amount of energy needed to kill cells when it is linked to the cell wall is ten times lower, according to further study. The demise of actin filaments and, ultimately, cell apoptosis (cell death), are the results of cell death caused by plasma-wall disintegration and the subsequent inflow of calcium. According to research, the efficacy of photothermal treatment with gold nanorods is enhanced when the nanoparticles are injected intravenously rather than subcutaneously into cancer cells. A single injection of PEG-coated nanorods rendered the laser cells fully inoperable when subjected to laser irradiation, according to Bhatia's study [1-5]. Tumor recurrence was not detected until 50 days subsequent to the examination.

Photothermal therapy with gold nanocages

It was recently outlined how gold nanocages may be used for photothermal therapy. About 55 % of the breast cancer cells were killed in an *in vitro* experiment using 40-nanometer nano cells and 5 min of 6.4 w/cm^2 laser light. All melanoma cancer cells inside the capsule were murdered in another experiment using 30-nanometer gold nanocages linked to anti-EGFR and a 40 w/cm^2 laser. Complete photothermal corruption with 43-nanometer nanocages linked to this counteracting chemical is what the outside world envisions. Gold nanorods outperform nanocages and nanoshells in 2 respects when compared to the other 2 structures that may undergo photothermal treatment in the near-infrared region [1-5].

1) The method of producing nanorods is quite simple; following an acceptable protocol, these structures are assembled with specific and movable point dimensions in a reasonable 2 h at room temperature. When manufacturing nanoshells, it is particularly challenging to get a uniform thickness around the silica core. Nanocages, on the other hand, need a starting point of around 150 °C for 20 h when generating silver nanotubes.

2) The high blood circulation time of gold nanorods is a result of their geometric anisotropy. Subsequent experiments in mice using nanorods coated with PEG show a blood half-life of 17 h. The fact that bar nanostructures binds to certain cellular ligands makes cell authoritative more appealing than circular structures, which is noteworthy in addition to the previous point.

Magnetic dissipation processes that generate magnetic heating

When an alternating magnetic field is applied to magnetic particles, the dissipation of their magnetic fields causes a rise in temperature via a number of mechanisms, including 1) hysteresis, 2) Neel relaxation, and 3) Brown relaxation. The next section provides a summary of these procedures [21,94].

Diamagnetic

Electrons linked in the orbitals are the source of diamagnetic characteristics. Copper, silver, gold, carbon, water, and polymers are just a few examples of the numerous materials that lack magnetic characteristics due to the presence of paired electrons. The rearranging of electron orbitals in these compounds makes them exhibit a modest repulsion when exposed to

an external magnetic field. The repulsion of diamagnetic materials to an applied field is less than that of paramagnetic and ferromagnetic materials. **Figure 23** shows that under normal conditions, the atoms in these materials do not possess magnetic moment. However, when subjected to a magnetic field, they undergo a weak formation and alignment of magnetic moment. This weak magnetic moment goes away when the magnetic field is taken out, and the material goes back to how it was before.

Scientific theories propose that atomic electrons occupy discrete areas known as orbitals. There are only 2 electrons in each orbital, and they're positioned opposite the spins, which allow the electron to spin around itself. When an external magnetic field is applied to a diamagnetic compound, a change happens in the orbitals of the coupled electrons. One electron's speed of rotation around the compound decreases while the other's speed increases. As a result, the magnetic dipole moment appears relatively weak in the direction opposite the external field (**Figure 23**). Once the external field of action is eliminated, the magnetic characteristics of these materials will also vanish. A vacuum has a higher magnetic permeability than diamagnetic materials. The term "diamagnetic" describes any substance that does not include another magnetic property. Diamagnetic means that superconducting materials do not allow a magnetic field to be transmitted through them [23-25].

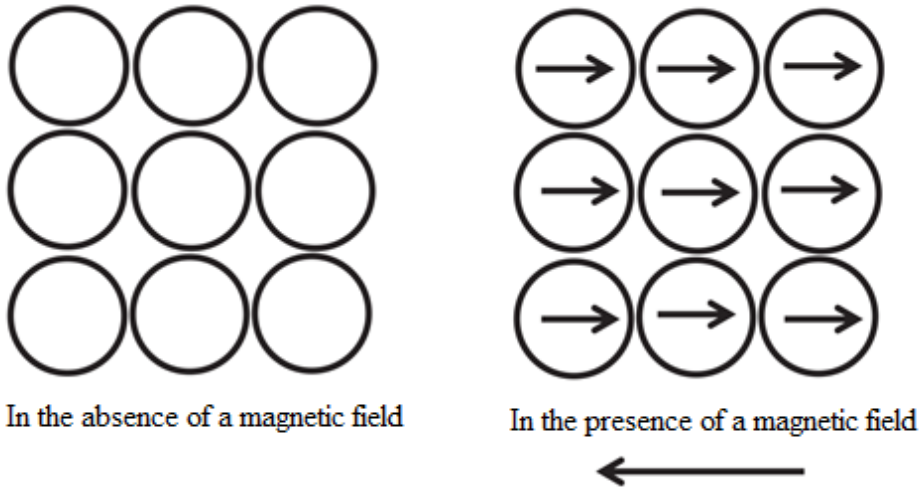

Figure 23 Diamagnetic substance atomic torque orientation schematic [23].

Paramagnetism

When an external magnetic field is applied, the unpaired electrons in paramagmatic substances (including tannium, magnesium, and lithium) align with the field and increase its strength. **Figure 24** shows that these compounds have a zero net magnet because the torque distributions are random and cancel each other out. These materials acquire a weak magnetic property when subjected to a magnetic field, which causes a number of torques to spin in the field's direction. Note that diamagnetic qualities are frequent and exist in paramagnetic materials as well, due to the fact that all materials, even paramagnetic ones, contain paired electrons. The paramagnetic property always triumphs over the diamagnetic one, nevertheless, since the magnetic property's intensity is much greater than the diamagnetic property's intensity [26]. To rephrase, some of the paramagnetic property is used to offset the diamagnetic property, therefore the quantity of paramagnetic qualities actually seen is more than the amount experimentally measured. Thus, it is customary to adjust the quantity of paramagnetic property (i.e., compute the compensated value and supplement it with the experimental value). Additionally, ferromagnetic materials include unpaired electrons and, when subjected to an external magnetic field, their atomic magnetic moments are ordered in a single direction (**Figure 24**). Iron, nickel, and cobalt, for example, all

have crystal structures that allow for the coupling of moments and direct contact. Thus, the magnetic characteristics of these materials are maintained even when the presence of an external field is eliminated. Hard magnets are another name for materials that keep their magnetic characteristics even when no external field is present. These materials become strongly magnetized when subjected to a weak magnetic field, and they retain some of their magnetism even after the field is removed. There is a tendency for the vectors of neighboring magnetic moments to align and be of comparable magnitude in ferromagnetic materials [27,28].

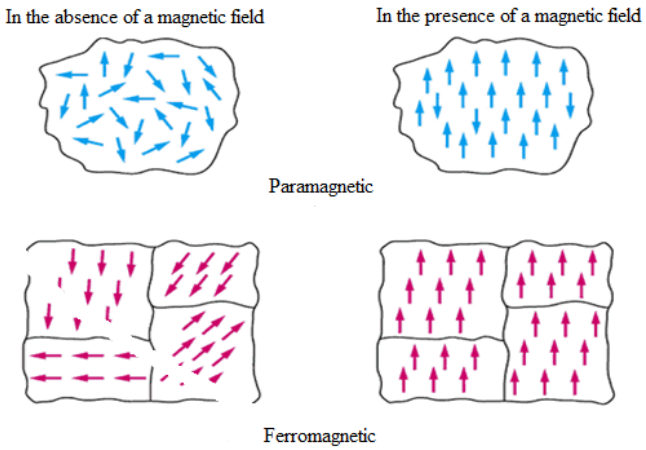

Figure 24 Orientation of atomic moments in paramagnetic and ferromagnetic materials [27].

Antiphromagnetism

Antiferromagnets are compounds with uniformly distributed atomic magnetic moments that point in opposing directions (**Figure 25**). The overall magnetic moment is 0 in these substances. When these materials are subjected to a magnetic field, their torques becomes stronger in the field's direction and they display a weak magnetic characteristic. At most cases, these materials consist of a pair of atoms with matching magnetic moments and directions, arranged at distinct atomic positions within the crystal lattice. They have no net magnetic moment because of this. Chemicals such as CuCl2, NiO, CoO, and MnO are antithrombogenic [29,30].

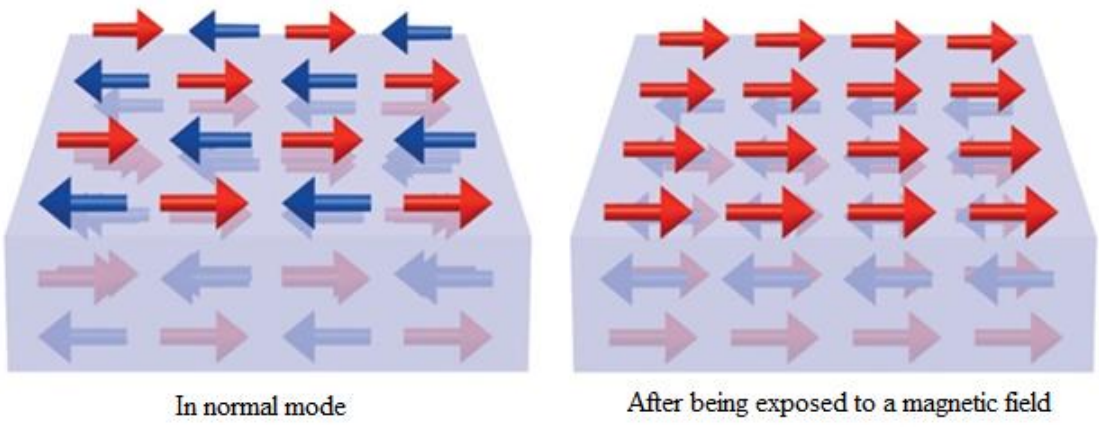

Figure 25 Orientation of torque of atoms in antiferromagnetic materials [29].

Free magnetism

The neighboring magnetic moment vectors in these compounds are sized differently and oriented in opposing orientations (**Figure 26**). Like anti-ferromagnetic materials, free-magnetic materials exhibit this feature; however, free-magnetic materials have an

uneven distribution of magnetic moments and a structure that includes 2 or more kinds of atoms or ions. A high level of electrical resistance and electrical insulating properties characterize the majority of ferromagnetic materials. This class includes a family of permanent magnets called ferrites [31].

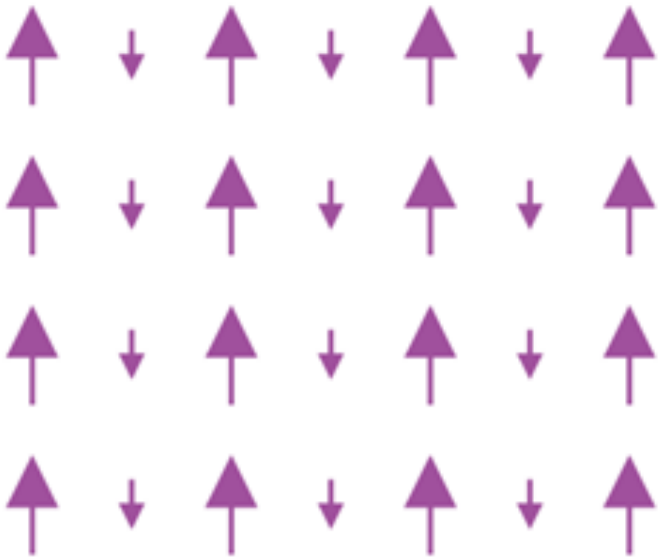

Figure 26 Orientation of the torque of atoms in ferromagnetic materials [31].

Superparamagnetic is a strange phenomenon

Ferromagnetic and ferromagnetic nanoparticles exhibit superparamagnetic properties at very microscopic levels. Almost always, magnetic nanoparticles with room-temperature dimensions smaller than the so-called single-domain magnetic field (20 nm for iron oxide) exhibit superparamagnetic characteristics. A few nanometers to a few tenths of a nanometer is the size of the magnetic field that is produced by different materials. The orientation of a cluster of spins is uniform in a magnetic field. These domains are divided by a wall of domains. The shape and nature of the spheres determine their breadth and energy of the walls (**Figure 27**). To review, a ferromagnetic substance or other magnetic item may take on magnetic characteristics when it is placed in a magnetic field. However, going back to a condition devoid of magnetic qualities does not occur entirely and spontaneously upon removal of the magnetic field. Because this material is magnetic, a magnetic field must be applied externally in order to return it to its initial condition. The inertness of magnetic materials to undergo magnetic phase transformations is known as magnetic coactivity. Based on data from both lab and field research, **Figure 28** shows the correlation between compulsion and particle size. As can be shown in **Figure 28**, the strength of magnetic induction diminishes with decreasing size of magnetic compounds, which usually include several domains, or multi-domains. The PUFA compounds undergo a transformation at a certain crystallite level into mesoporous particles, which are then shrunk even further to produce superparamagnetic particles. As a result, the nanoparticles exhibit a very attractive magnetic quality, as if they were individual paramagnetic atoms with enormous magnetic moments. By nature, superparamagnetic compounds do not exhibit magnetic properties; but, when exposed to an external field, they may undergo a magnetic transformation [32-35].

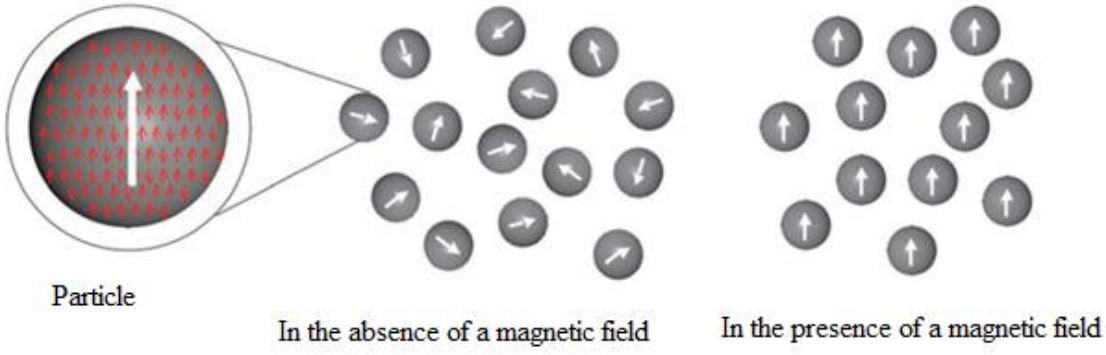

Figure 27 Schematic of a superparamagnetic particle [32].

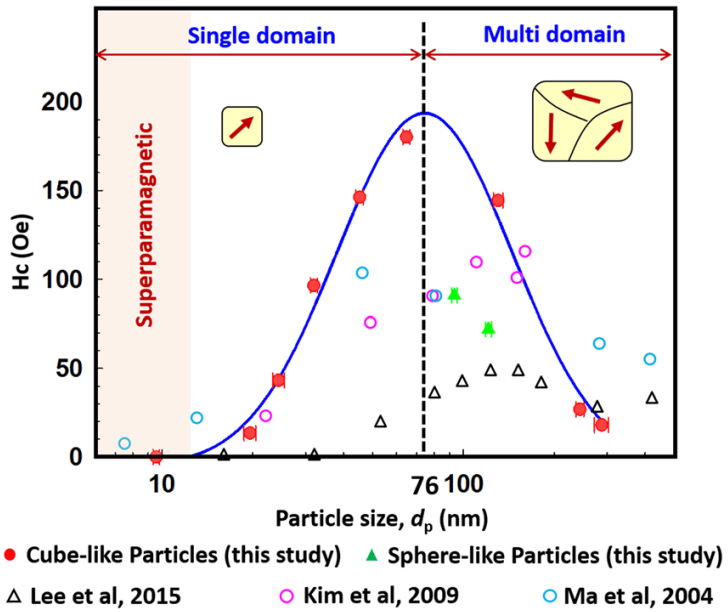

Figure 28 Scheme of the dependence coactivity of the binding property on the size of the nanoparticles [39].

Special properties of magnetic nanoparticles

Nanoparticles' magnetic properties are influenced by 2 main reasons: Finite-size effects and surface effects. These 2 causes cause nanoparticles to have diverse characteristics. The direct impact of shrinking nanoparticles on bond energy is a result of processes like quantum confinement, which is mostly associated with changes in atomic structure. Nevertheless, the disruption of crystal symmetry at the particle boundary is associated with the surface effect [35].

Size effect

Think about (**Figure 28**) when you talk about how the 2 single-domain and superparamagnetic ranges' sizes affect things. A multi-sphere structure with magnetic zones separated by spherical walls is characteristic of massive magnetic particles. The process of forming a sphere's wall involves balancing the energies of the magnetostatic field and the domain wall. There is a direct relationship between the particles' volumes and their magnetostatic energy, and between the area of their shared seasonal season and the energy of the sphere wall. In the single-basin condition, the magnetostatic energy must be balanced by forming the basin wall, and this process becomes more energy intensive as particle size decreases, leading to the creation of a critical volume. If a particle is contained inside a single sphere, it may be evenly magnetized by directing its spins in a certain direction. However, if the spheres are not in motion, their magnetic property can

be turned backwards by turning its spins in the opposite way. This explains why even extremely tiny nanoparticles exhibit such strong compulsivity [36].

Surface effect

A smaller particle will have a higher surface-to-total atomic number ratio as its size drops. This demonstrates how significant the surface and, by extension, surface effects, are. It is expected that surface spins will have a significant impact on nanoparticles' magnetic behavior because of the high surface-to-bulk atomic ratio. In terms of structural features like crystal constant and atomic coordination, among others, local symmetry overlap (where symmetry is defined as the equality of the number of surface spins and other spins in the particle) impacts these dimensions. How much the spin symmetry is broken is proportional to the particle size and the surface deformation. Internal atoms have one kind of environment while surface atoms have another. The surface of the nanoparticles becomes magnetic (ferromagnetic or antiferromagnetic) due to the aforementioned alterations brought about by the distortion of the symmetry of the spins on their surface. Ferro magnets, formed by surface effects, may be found in metal nanoparticles and oxides. When exposed to ambient temperature, non-magnetic nanoparticles like cerium oxide (CeO2) and aluminum oxide (Al2O3) may cause the irreversible reorientation of surface spins, resulting in magnetic residues. It is worth mentioning that the surface effect has the potential to either decrease (in the case of oxide nanoparticles) or enhance (in the case of metal nanoparticles, like cobalt) their magnetism. The existence of a magnetic dead layer and spin-glass (**Figure 29**), which are disorders of magnets or magnetic particles where the spins are not distributed in a normal way, are the factors that reduce the oxide's magnetism [37-39,94-100].

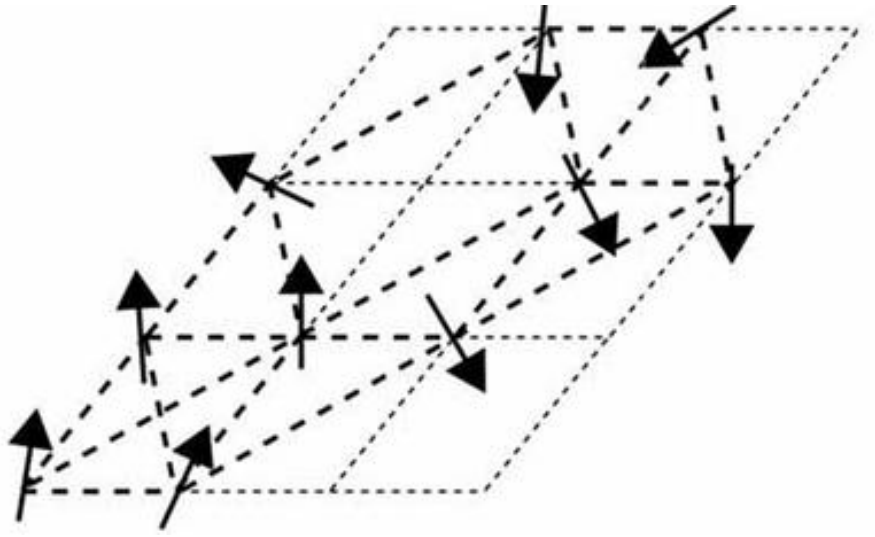

Figure 29 Scheme of spin-glass behavior [37].

MNPs and targeted provision of medications

Medicinal cell, protein, and nucleic acid research has been very fruitful recently [101-111]; the inherent adaptability of these biotherapeutics makes them promising candidates for application in future treatments. The unfortunate reality is that biotherapeutics are not fully used due to inadequate distribution channels. To get around this, new magnetically driven delivery devices were developed to allow for the precise, rapid, and localized administration of biotherapeutic treatments [112-127].

Review the long-term biodegradability and clearance of gold nanoparticles from the body to address potential accumulation concerns

Gold is a very useful nanomaterial in many clinical applications, but its poor biodegradability can affect its long-term physiological clearance. Large gold nanoparticles (20 - 200 nm), necessary for long blood

circulation times and critical tumor localization, often show little or no dissolution or excretion. This issue can be improved by incorporating smaller gold particles into larger units, but precipitation may be slower due to incomplete gold dispersion. In this study, we describe a new gold nanoparticle formulation capable of environmental degradation [269]. Ultrasmall gold nanoparticles are coated with thiolate dextran and incorporate hydrophobic acetal groups by direct covalent attachment to the dextran. This hydrophobic exterior allows gold to be tightly packed into approximately 150 nm polymer micelles. Upon contact with an acidic environment, the acetal groups are cleaved, rendering the gold nanoparticles highly water soluble and destabilizing the micelles. Within 24 h, extremely small, water-soluble gold particles are released from the micelles and readily disperse. Micelle disassembly and gold nanoparticle dispersion were imaged in cultured macrophages, demonstrating that micelles treated with the micelle facilitated physiological clearance of gold, with >85 % removed from the liver in 3 months [270,276-278]. These particles represent a novel nanomaterial formulation and overcome significant unresolved barriers to the clinical application of gold nanoparticles. Gold nanoparticles (AuNPs) are one of the most intensively studied Nano formulations due to their ease of manipulation of morphology and surface chemistry, as well as their potential for a variety of clinical applications. Gold has attracted considerable interest as a therapeutic agent, particularly in the field of oncology, for applications such as radio sensitization and photothermal therapy. It has also been studied in a variety of biomedical imaging techniques, including computed tomography (CT), photoacoustic imaging, and surface-enhanced Raman scattering. In addition, gold has been complexed with many other drugs and imaging agents as a scaffold for targeted delivery and multimodal activity. Most AuNPs and other nanomedicines are intended for injection into peripheral veins. Once in the bloodstream, many particles are eventually phagocytosed by macrophages in the liver and spleen. The ability of particles to target specific biological compartments depends on their physicochemical properties [270]. For example, particle shape and surface chemistry can affect interactions with serum proteins and cell membranes. Factors such as charge, hydrophobicity, and specific molecular markers can promote rapid uptake by phagocytes, whereas neutral hydrophilic coatings such as polyethylene glycol (PEG) slow phagocytosis, resulting in longer serum circulation times. Particle size also has a significant impact on serum half-life. AuNPs smaller than ~10 nm tends to be rapidly cleared by the kidney, whereas particles larger than ~200 nm promote sequestration in the liver and spleen. Prolonged serum circulation can have many desirable effects, including increased particle localization within tumors. This phenomenon is known as the enhanced permeability and retention effect (EPR) and can result in circulating nanoparticles extravasating through leaky tumor vasculature and persisting due to poor lymphatic drainage [271].

Ethical and regulatory considerations associated with the clinical translation of gold nanoparticle-based therapies

Gold nanoparticles show precise physicochemical features, which may be beneficial for healing purposes. After a long time of preclinical progress, gold Nano constructs are slowly however gradually transitioning into scientific trials. Although first of all notion to be “magic golden bullets” that might be used to deal with a huge variety of illnesses, modern consensus has moved in the direction of a greater practical approach, in which gold Nano formulations are being investigated to deal with particular disorders [272]. These healing programs are dictated with the aid of using the pharmacokinetics and biodistribution profiles of gold nanoparticles. Here, we examine the modern scientific panorama of healing gold Nano constructs, speak the shared traits that allowed for his or her transition from bench to bedside, and have a look at present hurdles that want to be triumph over earlier than they may be authorized for scientific use. DNA methylation is 1 mechanism of epigenetic law of gene expression and versions withinside the methylation of the promoter areas of genes are related to loads of human illnesses [273]. The discovery and alertness of the CRISPR-Cas gene-enhancing gadget has created new possibilities now no longer simplest for the usage of it to govern genomes for healing purposes, however additionally to broaden healing modalities via methylation-particular epigenome modification. Although there’s vast ongoing

debate round human genome enhancing, mainly of the germline, there was noticeably little dialogue of the ethics and law of human epigenome enhancing (e-GE) of somatic cells the usage of this technology. There are presently no human trials the usage of e-GE registered in ClinicalTrials.gov, however there are some of preclinical processes shifting in the direction of human checking out withinside the close to future. Given the tangible opportunity of ameliorating loads of illnesses and situations with e-GE, it's miles vital to have a look at the associated moral and regulatory troubles. To do so, we first cope with troubles associated with feasible undesirable results of somatic mobileular e-GE at the germline. Next, we have a look at 3 huge doable processes to the scientific translation of somatic mobileular e-GE [274]: (1) concentrated on disorder genes; (2) augmenting present therapies; and (3) improving phenotypic traits. We then describe a number of the medical and moral uncertainties of those processes and their implications. Finally, we speak a few related regulatory troubles. It now seems probable that somatic mobileular e-GE may be utilized in a way this is regular with different somatic mobileular and gene therapies. The obvious loss of germline results shows that, even though "gene-enhancing" technology are probable to be employed, e-GE have to be regulated beneath Neath present frameworks for scientific studies related to novel mobileular and gene therapeutics, focusing interest at the results instead of the mechanism of the interventions. In this context, player protection is paramount at some stage in the checking out and registration lifestyles cycle. Despite the inherent uncertainties of any new scientific technology, accomplishing ethically sound e-GE scientific translation studies might appear to be appropriate, mainly for critical illnesses and situations in which there aren't anyt any opportunity interventions, or in which present remedies are sub-optimal. Having stated that, regulators and different coverage makers may also want to recollect the character of e-GE and the capacity reversibility of adjustments made to gene expression [275].

Conclusions and future prospectives

1) The use of laser hyperthermia alone is a problematic and ineffective treatment option. There is a lot of hope for the future of nanoparticle cancer therapy because to the many studies those have used gold nanoparticles. Materials are classified according to their magnetic characteristics in this study, which includes diamagnetic, paramagnetic, ferromagnetic, antiferromagnetic, and ferromagnetic materials. Here, magnetic nanoparticles and the characteristics of these particles are presented. By studying magnetic compounds and adding their qualities into our understanding of superparamagnetic behavior, we were able to deduce how size and surface affect the magnetic properties of materials and how magnetic nanoparticles work. Because of their very tiny size and high surface-to-volume ratio, nanoparticles exhibit distinct physical and surface characteristics compared to bulk materials. Nanoparticles have many modern-day uses in engineering, the medical field, industrial processes, and the pure and applied sciences. Important uses for magnetic nanoparticles include intelligent medication delivery, ferroalloys, magnetic nanocomposites, and data storage. In the last ten years, MNPs—essentially SPNs—have shown to be a useful tool for enhancing the efficacy of magnetic resonance imaging (MRI) techniques, promoting the release of beneficial substances, and interfering with the degradation of cancer cells and biofilms. The development of targeted targeting methods has shown that MNPs can target certain tissues, including cancer cells, opening the door to the possibility of a more personalized, cutting-edge approach to MNP-mediated therapy. There are many reviews that reveal various methods of fabrication and synthesis techniques for MNPs, basically classified into the following categories: (1) Physical methods; (a) size reduction to the needed nanometer range and dispersing in an aqueous medium (by classical colloidal routes) and (b) condensations of the precursor from either a liquid or gaseous phase. Very important disadvantage of the method is the difficulty of achieving the desired particle size and shape. A laser ablation or evaporation synthesis method prove to be an extremely effective method of creating powders with relatively uniform sizes of course materials and iron blocks. (2) Wet chemical preparation methods: includes chemical co-precipitation, sol-gel and hydrothermal reactions, flow injection synthesis, polyol methods, electrochemical and aerosol/vapor methods, thermal decomposition, hydrolytic and nonhydrolytic

methods, microemulsion and laser evaporation methods. (3) Microbial methods – MNPs form in a biomineralization process. Also, developments in attractive hyperthermia have caused near complete tumor recurrence and the desensitization of drug-resistant bacterial strains to anti-microbials. These features make MNPs stand out as highly adaptive and versatile, making them suitable for use in a broad range of biological contexts. There has been substantial progress in this area, and the use of MNPs is expected to become a staple Figure in the prospective treatment of both cancer and resistant disorders; nevertheless, their use in cancer diagnosis and therapy is currently limited. Despite cancer nanotheranostics being a relatively new area of study in the last decade, it shows great promise for widespread use in tailored pharmaceutical oncology for cancer therapy, according to this topical review. A closer look at the illness's microbiological environment, as well as stimuli-responsive nanomedicines and co-delivery of pharmaceuticals using nanocarriers, is warranted in light of the present knowledge and findings. In addition, support efforts should be focused on developing a new preclinical model that might lead to more precise clinical consistency. As a result, further clinical studies including nanotheranostics should be conducted. Concerning nanomaterials, there has to be further research into targeted tumour and cancer marker placement in human serum, as well as the design and combination of functionalized nanoparticles in dynamic delivery systems.

2) Nanomedicine has several programs in theragnostic-primarily based totally medicine. In the beyond few decades, many research has investigated the usage of nanomedicine in scientific studies. Although extra studies are important to verify a medicinal product for use withinside the scientific remedy platform, on the moment, there are some of nanotechnology merchandise that have already entered the client marketplace serving as pills and sensors. Hybrid GNPs are metallic-primarily based totally nanoparticles used withinside the scientific remedy of most cancers and infectious sicknesses. GNPs take numerous diverse molecules, together with pills, genes, antibodies, polymers, and different ligands, for concentrated on or turning in molecules. Today, multifunctional hybrid GNPs are used as theragnostic marketers which offer diagnostic and healing purposes, simultaneously. Furthermore, GNPs set off plasmonic photothermal remedy as a non-invasive technique to deal with diseased cells. All of those programs of GNPs stem from their specific optical, chemical, and bodily properties. However, similarly precise and correct research are had to endorse a complete technique. For example, the hybrid GNPs may be conjugated or immobilized with the aid of using pills, genes, antibodies and biocompatible polymers in an effort to supply and goal molecules or picture marketers. Moreover, extra major research wants to consciousness at the floor functionalization of GNPs to boom the protection and decrease the toxicity of GNPs together with the layout treatments that typically stand up in photothermal and photodynamic treatments. Some researchers consider that the toxicity of GNPs is associated with the concentration, shape, and length of the nanoparticles which are utilized in research. This functionalization has a right away connection to cell connectivity and uptake. Today, many research are being performed to offer and optimize an inexperienced technique for the synthesis of GNPs. Nevertheless, 1 essential query is how a multifunctional machine of hybrid GNPs (with the proper length and shape) may be organized to be used in diagnostic and healing programs at the same time as having the least toxicity and maximum effectiveness. Future investigations on theragnostic-primarily based totally GNPs programs must be achieved to discover molecular mechanisms and their dating with the floor change of nanoparticles, gene expression, protein production, and signaling pathways, due to the fact cellular demise mechanisms have inseparable hyperlinks with the cited items. According to the above discussions, the need for a complete look at appears inevitable to cowl all of the indexed items. We consider that, because of the massive boom of studies performed among 2013 and 2016 (mentioned above), similarly improvement and scientific studies are sure to arise in an effort to find out a unique and secure approach for theragnostic application. At present, there are various applicants going thru diverse stages of *in-vitro* and *in-vivo* investigations. Among the diverse programs of hybrid GNPs, PPTT is similarly expanded. Certainly, PPTT in aggregate with chemotherapy or PDT offers a synergistic effect, and we have confidence that it may

reap the imaginative and prescient of imparting an operational technique of remedy of sicknesses withinside the not-too-remote future. In evaluation to the cited items, the clearance and the interplay of GNPs with herbal biomolecules in more cell membranes or plasma are problems that have been much less addressed.

3) Magnetic nanoparticles show promising benefits for biomedical purposes as imaging contrast enhancement and targeted therapeutics for cancer treatment over conventional surgery, chemotherapy and radiation therapy. Modern medicine strives to discover improved methods of treating various diseases, focusing on a highly personalized approach. The major issue holding back the clinical translation is the lack of control in the different stages of preparation and insufficient tissue selectivity. In the name of biomedical progress, numerous modifications could be applied to therapeutic or diagnostic agents. The main purpose is to enhance their potential and overcome the limitations. There are improvements in controlling MNPs size, shape and surface modifications. Thanks to them, improved physical and biological properties are obtained, improved magnetic properties are gained, and tissue targeting is accomplished. The challenge, therefore, is to develop multifunctional nanomaterials that can be integrated into different therapeutic modalities using 1 nanoplatform, which is considered a new trend in recent nanomedicine research.

Abbreviations

NIR	near-infrared
OCT	Optical Coherence Tomography
RCM	Reflectance confocal microscopy
SLP	Specific loos power
GNPs	gold nanoparticles
EPR	enhanced permeability retention
LSPR	Localized Surface Plasmon Resonance
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
FWHM	full width at half-maximum
TEM	Transmission electron microscopy
ROS	Reactive Oxygen Species
DNA	Deoxyribonucleic acid
MCGs	methylated cytosine-guanine dinucleotides
MBD1	methyl binding domain protein 1
PDT	photodynamic therapy
PEG	polyethylene glycol
TGA	Thermo gravimetric analysis
CBA	capture antibody deposition
GNFs	gold nanoflowers
Vap	vapreotide acetate
CMC	critical micelle concentration
SPM	Superparamagnetic
DM	Diamagnetic
PM	Paramagnetic
FM	Ferromagnetic
GNSS	Gold nanostructures
MNPS	magnetic nanoparticles
SNPS	Silicon nanoparticles

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