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Multifunctional management of gold nanoparticles for improved applications

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***Abstract*---**Increasingly, nanotechnology has the potential to be applied in disease detection or treatment. Nanotechnology advancements have resulted in novel and improved biomedical nanomaterials. Liposomes, polymeric micelles, graphene, carbon nanotubes, quantum dots, ferro ferric oxide nanoparticles, gold nanoparticles (Au NPs), and so on are some of the most commonly used nanomaterials in biomedical applications. Because of its unique

optical, electrical, sensing and biological capabilities, Au NPs have been regarded as the most fascinating nanomaterial. Medical imaging, drug administration and tumour therapy are all possible applications of Au NPs in the early identification and diagnosis and treatment of illnesses. This review focuses on some recent breakthroughs in the management of Au NPs as drug carriers for the intracellular delivery of therapies and as molecular nanoprobes for the detection and monitoring of target molecules.

***Keywords*---**Molecular nanoprobes, imaging, detection of disease, drug delivery, gold nanoparticles, Au NPs.

1. Introduction

Recently, the use of nanotechnology in the biomedical field has received attention [1]. The properties of nanomaterials, which have a diameter ranging from 1 to 1000 nm, are quite different from those of tiny particles or bulk materials. Many biomedical applications could benefit from their huge specific surface area and high surface activity, as well as their excellent antioxidant properties, biocompatibility and suitability for molecular modifications. Liposomes, polymeric micelles, graphene, carbon nanotubes, quantum dots, magnetic nanoparticles, metallic nanoparticles, and so on are currently prevalent nanomaterials employed in biomedical applications. Using them has been demonstrated to have a substantial impact on the outcomes of therapy.[1]

The biomedical application of metallic nanoparticles, particularly gold nanoparticles (Au NPs), has piqued attention among the many nanomaterials listed above since they offer obvious advantages. In the first place, we can readily synthesise a wide range of Au NP shapes, from the spherical to the rod-like to the cage-like, from the 1 nm to more than 100 nm range. In terms of optical and electrical properties, the shape and size of Au NPs have a significant impact. Au NPs, because of their negative charge, are ideal for functionalization by many kinds of biomolecules, such as drug molecules, genes and ligands [3]. Au NPs, on the other hand, are biocompatible and free of toxicity. Fourth, the surface effect, ultra-small size, and macroscopic quantum tunnelling effect of Au NPs [5] are all distinguishing features of these nanoparticles. It is because of these qualities that Au NPs have emerged as the most promising material for biomedical applications such as biosensing. We'll focus on the most recent studies on the use of Au NPs in molecular imaging and drug carriers for disease therapy in this article. In-depth information has been provided elsewhere [6–8] on the most significant elements of the synthesis and usage of Au NPs in biosensing.

2. Synthesis and Biofunctionalization

Numerous approaches are available for the production of Au NPs. Au NP synthesis techniques have been thoroughly reviewed [9]. In this section, we'll give a quick overview. Colloidal synthesis is extensively used to create gold nanoparticles for biological applications. This method, which makes use of a metal precursor, a reductant, and a stabiliser, allows for easy control over the

nanostructures' dimensions, shapes, and optical properties. Below are a few examples of Au NP syntheses.

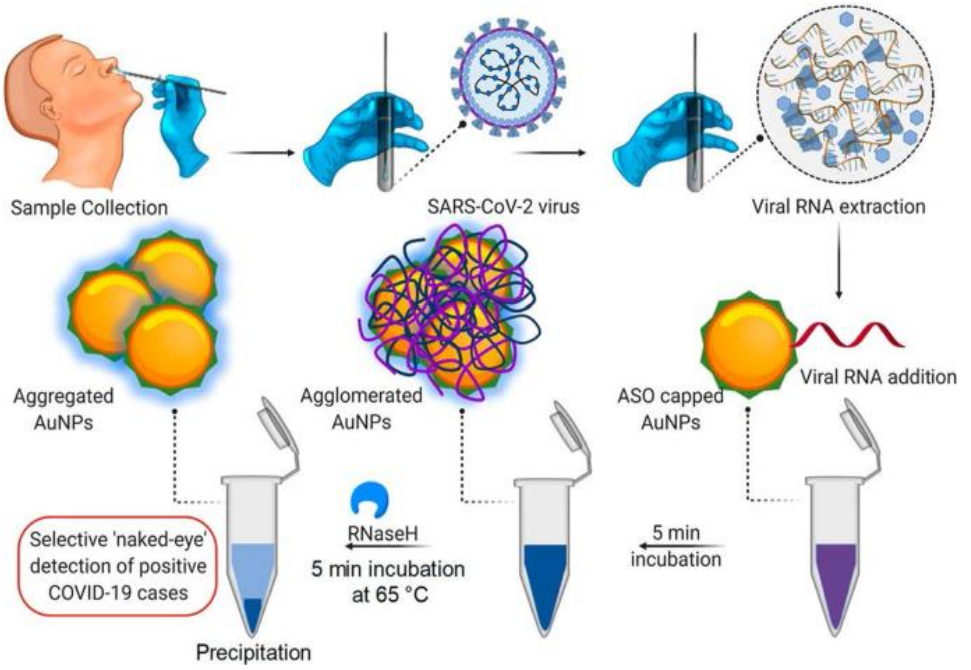

Figure-1

In drug delivery applications, spherical gold nanoparticles (Au NSs) are one of the most commonly employed gold nanostructures. The reduction of aqueous chloroauric acid with sodium citrate allows for the easy synthesis of a large number of Au NSs with a rather high single dispersion. The size of spherical nanoparticles can be adjusted by altering the stoichiometric ratio of chloroauric acid and sodium citrate [10]. Citrate is both a reducing agent and a stabiliser in this process.

Photothermal and near-infrared (NIR) applications frequently use the gold nanorods (Au NRs). Au NRs can be synthesised in two general ways: seed-mediated and seedless. A solution of small seeds (3–5 nm) is frequently required for the seed-mediated growth approach. Au NRs are formed via anisotropic reduction of Au+ at the nucleation sites provided by the seeds. In order to alter the length and aspect ratio of Au NRs, the concentration of AgNO3 can be increased. In order to induce seed development and growth of Au NRs in the seedless approach, an acidic pH of the growth fluid is required [12].

Biofunctionalization

Au NPs' biological applications benefit greatly from their ability to be functionalized on the surface. It is possible to functionalize the surface of gold nanoparticles with biomolecules such as DNA, peptides, antibody, and many more. Interaction can be divided into two categories. There are two types of interactions: noncovalent and covalent. Electrostatic interactions, hydrophobic

trapping, and van der Walls forces all play a role in noncovalent alterations. Because of this connection, the biomolecule is unable to attach itself to numerous chemical changes that may undermine its primary, active mode. Biomedical research require surfaces that can withstand washing and incubation processes, however the binding is not strong enough to produce stable surfaces. This alteration should be used with consideration for the ionic strength and pH of the surrounding media. The stability and reproducibility of covalent changes, in contrast, are improved by the introduction of linker molecules or click chemistry, which use an immediate chemical interaction. In addition to their great salt tolerance and excellent temperature stability, covalent alterations are also exceptionally resistant to oxidation. A lot of synthesis effort on the ligands is required for covalent changes, which are typically more difficult. Because of the relative ease with which nanoparticle surfaces can be modified via noncovalent and covalent means, they can be employed in bio diagnostic and biosensing applications.

Au NPs as Drug Delivery Carriers

When it comes to delivering drugs to the body, researchers are intrigued. Biologically active medication can be released at a specified rate and place through the method of drug delivery. Specific drug delivery methods must be improved for clinical use now. Nanomaterials hold immense promise for the delivery of multiple, locus-specific drugs to the disease locus. Specifically, Au NPs have shown a great deal of potential as drug delivery platforms. Antibodies, vaccines, and nucleotides can be delivered to their targets using Au NPs, which can be activated by light (internal) or biological stimuli (external) to control the release of pharmaceuticals (external**).**

Au NPs for Drug Delivery

In the treatment of end cellular disorders, Au NP-drug conjugates are critical [13,14]. They have the potential to enhance the efficacy of pharmaceuticals. There are a number of ways in which antibiotics or other therapeutic compounds can be directly conjugated with Au NPs. Methotrexate with colloidal Au at a size of 13 nm, for example [15]. Anticancer medicine Methotrexate is an analogue of folic acid, which inhibits the growth and reproduction of cancer cells. After an overnight incubation, the carboxylic groups on the methotrexate molecule can attach to the surface of Au NPs. Methotrexate bound to Au NPs has been shown to have a greater concentration than methotrexate bound to Au NPs in the same volume. A pH-sensitive linker was used in another work to attach doxorubicin (DOX) to 30 nm gold nanoparticles (NPs). Intracellular release of DOX from Au NPs can be activated by acidic organelles with this sort of DOX-Au NP attachment. In drug-resistant tumour cells, this allowed for a rapid rise in intracellular DOX concentration [16]. (Figure 1). Molecular 2017, 22, 1445 3 of 13 vaccinations, or nucleotides, onto their targets and control drug release by biological stimuli (internal) or light activation (external).

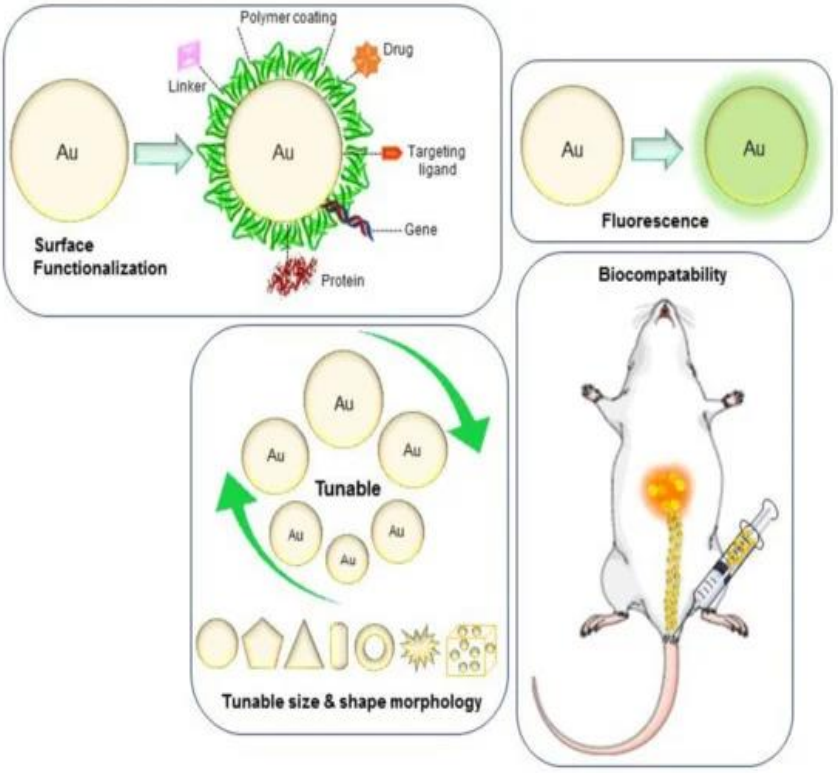

Figure-2

In the treatment of endocellular disorders, Au NP-drug conjugates are critical [13,14]. They have the potential to enhance the efficacy of pharmaceuticals. Ionic or covalent bonding, as well as physical absorption, are all methods that antibiotics and other therapeutic compounds can use to attach directly to Au NPs. Methotrexate with colloidal Au at a size of 13 nm, for example [15]. Anticancer medicine Methotrexate is an analogue of folic acid, which inhibits the growth and reproduction of cancer cells. After an overnight incubation, the carboxylic groups on the methotrexate molecule can attach to the surface of Au NPs. Methotrexate bound to Au NPs has been shown to have a greater concentration than methotrexate bound to Au NPs in the same volume. A pH-sensitive linker was used in another work to attach doxorubicin (DOX) to 30 nm gold nanoparticles (NPs). Intracellular release of DOX from Au NPs can be activated by acidic organelles with this sort of DOX-Au NP attachment. Thus, the intracellular DOX concentration could be rapidly elevated, improving therapeutic effects in drug-resistant patients.

Poly ethylene glycol (PEG) can be used as a spacer to modify the surface of Au NPs. As a result of polymers' amphiphilic properties, gold nanoparticles are extremely stable under physiological settings and can be combined in a wide variety of ways. Numerous studies have shown that polymer-modified Au NPs have exceptional characteristics. Oxaliplatin's active components were linked to Au NPs by Wheate et al. for better drug delivery [17]. Thiolated PEG monolayers were applied on Au NPs, which were capped with carboxylate groups. [Pt(1R,2R-

diaminocyclohexane)(H2O)2] The PEG surface was coated with 2NO3 to create a supramolecular molecule. Tests on the platinum-tethered nanoparticles were conducted on the A549 lung epithelial cancer cell line, as well as on the HCT116 and HT29 colon cancer cell lines for cytotoxicity and drug uptake. Additionally, the platinum-tethered nanoparticles had cytotoxicity that was as good as or better than that of oxaliplatin alone in all cell lines, and they were able to enter the nucleus of lung cancer cells with remarkable ease. Non-specific endocytosis was used to rapidly absorb Au NPs in combination with courmarin-PEG-thiol [18]. It was discovered by Bhattacharya et al that the noncovalent bonds between Au NP and PEG-amines folic and acid allowed them to be easily targeted to cancer cells' folate receptors. Polymer-drug conjugates of folic acid with Au NPs, according to the scientists, could have a significant impact on the future delivery of folate receptor-targeted drugs or on targeted therapy [19]. Spherical Au NPs were modified using 3-mercaptopropionic acid (MPA). Imitation between the carboxylic group on the Au NPs and the amine end-groups on the PEG was subsequently used to join the MPA layer with NH2-PEGNH2. For nucleus-targeted administration, conjugation results in excellent stability in an electrolyte environment and great intracellular transport efficiency [20].

Au NPs for Gene Delivery

Gene therapy is a promising treatment option for both hereditary and acquired disorders [21]. As they are able to deliver all sorts of oligonucleotides, such as double-stranded DNA (dsDNA), single-stranded RNA and single-stranded DNA (ssDNA), recent research have shown that they could be quite effective in treating diseases. DNA and RNA delivery could benefit from the use of Au NPs. DNA is guarded by Au NPs, which keep nuclease from degrading it. Cell transfection and targeting can be assisted by them. Nanospheres and nanorods, as well as other morphologies of Au NPs, are now being employed for this purpose.

Intracellular gene regulators using oligonucleotide- and short interfering RNA-modified Au NP conjugates exhibit unique features. Activating immune-related genes and pathways in human peripheral blood mononuclear cells via covalent bonding of oligonucleotides is possible, but not in a permanent, lineage-restricted cell line. Findings such as these are critical for the creation of oligonucleotide-modified Au NPs conjugates in translational research and for therapeutics and gene delivery technology [22].

An investigation of Au NPs functionalized with cationic ammonium groups and electrostatically integrated into the plasmid DNA was carried out as early as 2001. A composite particle protected DNA from degradation by enzymes and controlled transcription of T7 RNA polymerase, according to the results [23,24]. Mirkin et al. utilised citrate-stabilized, spherical Au NPs with ssDNA molecules functionalized with single or multiple thiol groups for gene silencing [25]. The structures of this combination were able to withstand degradation by proteases and a high degree of endogenous glutathione levels, allowing for effective cell uptake. Increased efficacy in gene silencing applications was achieved by improving the integration of complementary DNA with ssDNA grafted in.

Au NRs can also deliver siRNA to specific cells or tissues because of their size and shape-dependent optoelectronic characteristics. When Prasad and his colleagues attached Au NRs and cetyltrimethylammonium bromide to siRNA (against dopaminergic neuronal (DAN) cells' DARPP-32 gene), they examined how the conjugates were taken up by DAN cells. According to the results of dark-field and confocal microscopy, the Au NR-siRNA conjugates were shown to be effective at delivering siRNA to DAN cells, as evidenced by the 98% cell survival. Using Au NPs as innovative carriers to transport genes into neuron cells has also been proven in the study results. Polysodium 4-styrenesulfonate and polyallylamine hydrochloride nanocarriers were designed by Zhao et al. to deliver LSD1-targeting siRNA to human mesenchymal stem cells (MSCs) [27] to stimulate differentiation. [20, 21] (Figure 2). Using hepatocyte growth factor (HGF), the researchers were able to induce human MSCs to differentiate into hepatocyte-like cells after the Au NR-PSS-PAH-siRNA (Au NRssiRNA) nano-carriers were successfully internalised (HGF). Using their findings, more effective nanoplatforms for delivering siRNA for tissue regeneration therapy may be developed.

Au NPs for Protein Delivery

For protein delivery, Au NPs can also be employed as nano-carriers. Biomedical uses of Au NPs may be profoundly affected by the interfacial interaction between proteins and these nanoparticles. In the study of protein structure, shape, and stability, organothiol is an important molecular probe. Organothiol inclusion in protein-coated Au NPs should not be neglected in biological and biomedical areas because of its significant prevalence in biofluids containing serum plasma [28]. Chitosan has been used in prior research to functionalize Au NPs for insulin delivery [29]. Chitosan is a biopolymer that can stabilise Au NPs without being harmful. Adsorption of insulin on the surface of Chitosan-coated particles is highly effective for transmucosal administration. According to Rotello et al [30], cationic tetraalkyl ammonium-functionalized Au NPs recognise the anionic protein's surface and inhibit its activity. The protein-particle complex was treated with SH, which resulted in the release of free protein, revealing Au NPs as potential protein transporters. Prior to intravenous injection, Krol et al. employed Au NPs to couple either human serum albumin (alb-Au NP) or apolipoprotein E (apoE-Au NP). When compared to citrate-stabilized Au NPs, the results demonstrated that protein conjugation significantly reduced liver retention. According to their research findings, the stable conjugation of Au NP with albumin and ApoE prior to infusion boosts the specificity and effectiveness of NPs in sick target organs, which implies a possible function in nanopharmacology [31].

Au NPs for Vaccine Delivery

Prophylactic vaccination is one of the most effective medical therapies, reducing death and morbidity from a wide variety of infections by a significant margin across the globe. Even while traditional vaccines are incredibly effective, their manufacture and distribution are constrained. In recent years, gold nanoparticles (Au NPs) have been widely exploited as vaccination platforms because of their variable size, shape, and customizable surface features over traditional vaccine platforms.

Au NPs have been proposed by Nebaikina et al. for the development of vaccinations against tick-borne encephalitis [32]. The multivalent design of Au NPs boosted their ability to bind to their target receptors. Three surface-engineered Au NRs were employed by Chen's group as HIV-1 Env plasmid DNA vaccination adjuvants for HIV treatment [33]. Researchers at the University of California, Berkeley, have created aptamer-conjugated Au NPs that are particularly effective in inhibiting HIV reverse transcriptase [34]. The use of Au NPs in HIV/AIDS vaccine development was evaluated by Chen et al. [35]. There have already been a number of great studies on the subject [36–40].

The Release of a Drug from Au NPs via External Stimulus

Payload release in a spatial and temporal manner significantly enhances therapeutic efficacy. Using external stimuli (operated with the support of stimuli-generating processes, such as the application of light) or internal stimuli (operated in a biologically controlled manner, such as pH or glutathione) to release drugs from Au NPs, new methods to control drug delivery and release can be developed [41].

Au NPs release medicinal molecules mostly in response to external light stimulation. As an illustration, Chompoosor et al. demonstrated an unique monolayer of Au NPs for the research of controlled release of a model drug under UV light [44].. Noncovalently, the compartments of its monolayers included hydrophobic molecules. The dinitrobenzyl linker was broken by UV radiation, allowing the contained chemical to be released. A system exposed to UV radiation releases more medicines than one that is not exposed to UV radiation. UV irradiation can be used to regulate dye release. GNR@DOX was used by Li and his colleagues as a combination of chemotherapy and photothermal ablation to treat metastatic breast cancer [45]. The local temperature of GNR@DOX was significantly raised by laser irradiation, thereby liberating the DOX-loaded molecule. To encapsulate macromolecules like dextran, Caruso and his colleagues used microencapsulation technology. Au NP-doped capsule-shells, which can withstand near infrared (NIR) radiation. Laser (1064 nm) treatment freed the fluorescein isothiocyanate-dextran after the shell ruptured. For the treatment of breast cancer, Zhang and his colleagues developed an Au nanoshell and 10-hydroxycamptothecin (HCPT-NPs) core/shell nanoparticle [47]. The core-shell nanoparticle achieved complete tumour remission in a 4 T1 breast syngeneic mouse model with an irradiation power density of 1 W cm2 for 10 minutes and no significant weight loss in mice or tumour recurrence. When it comes to treating A549 lung cancer, a PEGylated multifunctional hollow gold nanoparticle (HGNP) with DOX was produced by Choi and colleagues [48]. The NPs are able to release DOX more effectively under NIR irradiation. The radiation-induced DNA double-strand breaks in A549 cells were a result of the sensitization of HGNP to 6 MV X-ray radiation in A549 cells. Experimentation in vitro indicated that the combination of high temperature and radiation was the most effective at destroying cancer cells. Pc 4 (silicon phthalocyanine 4), a rabies therapy medication, was attached to PEGylated Au NP conjugates in another study. Phototherapy begins when the Au NP-Pc 4 combination reaches the tumour location and the Pc 4 molecules are released from the nanoparticle's surface. [49]

Electroporation is another method for delivering genes from Au NPs using an external stimulation. In order to study gene transfer in vivo, Kawano et al. employed electrical pulses to induce Au NPs. Au NPs were incorporated into plasmid DNA and modified using mPEG-SH5000 as part of their study. The anaesthetized mice were then injected with the conjugates. Electrodes were applied to the left lobe of the liver after some time to confirm that the conjugates were well absorbed. Gene expression was found in the organs of major mice, according to the findings. Tenfold less DNA was detected in the mouse injected with unmodified DNA, but the detection rate was ten times lower. There was a striking correlation between the low transfection efficiency in the latter situation and the short breakdown duration of DNA in blood. With the help of gold nanoparticles, our study discovered a new and exciting method for optimising gene delivery.

Au NPs as Molecular Nanoprobes
Au NP-Based Molecular Diagnostics

Improved sensitivity, specificity, multiplexing, and turnaround times of molecular diagnostics have been achieved by the introduction of AuNPs. Since Au NPs have been widely used as sensing interfaces and labelling in bio-recognizing events for signal amplification, they've been studied elsewhere. In this section, we'll give a quick overview of the diagnostic potential of gold nanoparticles (Au NPs). As an example, Lu et al. have constructed the first DNAzyme-based metal sensors by attaching a fluorescent DNAzyme to Au nanoparticles [51]. Au NP core was covered with 39E DNAzyme shell, which was specific to uranyl ionisation. Using these DNAzyme-Au NP probes, the researchers proved that they may easily enter cells and serve as metal ion sensors in a cellulated environment. In order to better understand the distribution and localization of metal ions in biological systems, further development of DNAzyme-AuNP probes is needed. [52] Guo et al. produced aptamer switch probes with dual functionality for targeted cancer treatment based on Au NRs (Figure 3). ATP aptamer and the Ramos cell aptamer were immobilised on Au NR surfaces in their research. When the Au NRs were coated with the two aptamers mentioned, they were able to identify tumour locations with excellent specificity. Dox-carrying capacity was increased by inserting various GC-pair sequences into dsDNA ATP aptamers. Combining the roles of two aptamers enabled the detection of intracellular ATP and the transport of therapeutic molecules into target cells. Also used as sensing interfaces and as labels for ultra-sensitively detecting carcinoembryonic antigen are Au NP nanocomposites.

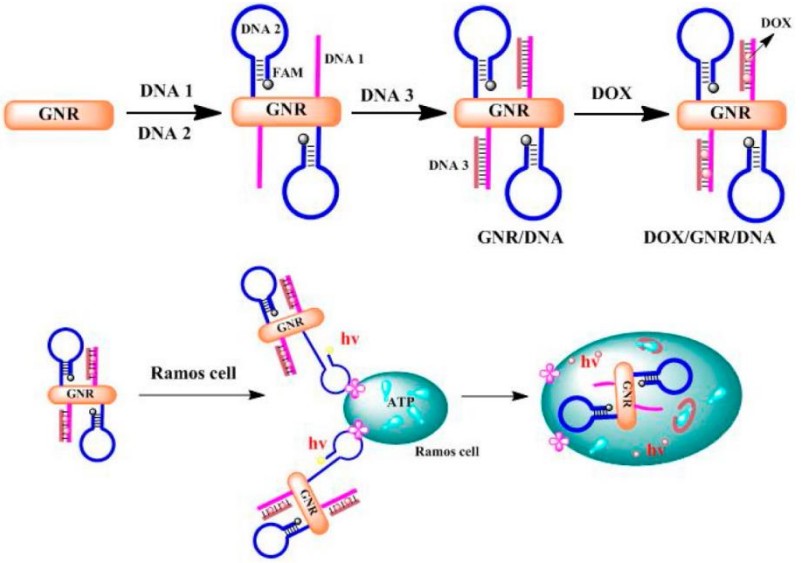

Figure 3. A targeted, delivery-quantification DNA assembly platform. This platform consists of Au NRs, DOX, and DNA sequences, which are composed of aptamer DNA strands and their complementary DNA strands [52]. Reproduced with permission from reference [52]. Copyright (2016), with permission from Elsevier.

Au NP-Based Molecular Imaging

In the last decade, molecular imaging technology has advanced quickly, allowing for the detection of disease with excellent sensitivity and specificity. It is now possible to diagnose disease using a wide range of imaging modalities including optical imaging, computed tomography (CT), ultrasound imaging, and magnetic resonance imaging (MR). Highlights in this section include SERS (surface-enhanced Raman scattering).

SERS provides the advantage of high sensitivity, high accuracy, no label, no harm, and no invasion for molecular identification compared to other imaging methods. A common application of Au NPs in the SERS approach is the monitoring of intracellular drug release and the probing of cellular compartments such as mitochondria, endosome and the cell nucleus with these molecules [55]. Using dimeric assemblies of spherical Au NPs, Fabris found a new form of tag with good biocompatibility for tumor-specific targeting and SERS-based detection [56]. Nanoparticles dimerized in close proximity to one another, resulting in a shorter active time and less cytotoxicity when compared to the monomer. Cell-internalized Au NP dimers were found to have a high degree of cellular recognition selectivity and to be exceptionally stable. Traditional fluorescence imaging is slower and less sensitive than SERS-based cell detection. Using peptide-functionalized Au NPs and SERS in living cells, Hu's team produced an all-new nuclear targeting nanoprobe [57]. They reported that the SV-40 large T nuclear localization signal (NLS) peptide integrated with AuNPs triumphantly reached the cell nucleus after incubation with Hela cells and transmitted the spatially localised chemical information of the nucleus and the signature of chemicals that

subsequently invaded. With its non-toxic, biocompatible characteristics and potential to be applied in cancer research, this new focused nanoprobe is a suitable method.

In terms of clinical applications, CT is widely employed because of its unmatched benefits of high spatial resolution and infinite penetration depth. An suitable CT contrast agent for Au NPs has unique physical, chemical, and biological features [59]. The A10 aptamer, which is directed towards the prostate-specific membrane antigen (PSMA), was coupled to Au NPs by Kim et al. [60]. These nanoparticles were shown to have high sensitivity and specificity in binding to PSMA-expressing prostate cancer cells. A10-Au NP conjugates can also be utilised to detect PSMA-expressing cancer cells in CT imaging, researchers observed. G5.NH2 dendrimers were used as templates by Zhang's group to produce gold nanoparticles (Au DENPs) encapsulated in dendrimers [61]. The acetylation of terminal amine groups forms Au DENPs with a neutral surface. Acrylated Au DENPs have the potential to be exploited as CT imaging agents for the in vitro imaging of the cancer cell model SPC-A1 and the in vivo imaging of a xenograft tumour model in nude mice. Au DENPs modified by PEG, which have high biocompatibility and could be used in CT imaging, have recently been shown [62]. As a result, PEGylated Au DENPs enabled not only CT blood pool scanning in mice and rats, but also CT imaging of a xenograft tumour model in nude mice. Au DENPs (Au DENPs-FA) modified by folic acid were recently reported to play a new role as nanoprobes for targeted CT imaging of human lung cancer in vitro and in vivo [63]. (Figure 4). In vitro microCT images show that SPC-A1 cells may be seen under X-ray following incubation with Au DENPs-FA. Xenograft tumours were also visible through imaging after intratumorally, intravenous, and intraperitoneal granule injection.

Accurate imaging requires the use of two or more imaging modalities. Gadolium-loaded Au DENPs (Gd-Au DENPs) were synthesised, characterised, and used for dual-mode CT/MR imaging by Shi et al. [64]. For CT/MR dual mode imaging of the heart and kidneys of mice and rats, an NP system that had two radiodense imaging elements of Au and Gd (III), Gd-Au DENPs, displayed both r1 relaxivity for MR and X-ray attenuation for CT, which contributed to the 45-minute time frame. The M-NPAPF-Au nanoprobe (co-loaded with Au NPs and an aggregation-induced emission (AIE) red dye into DSPE-PEG2000 micelles for dual-modal fluorescence/CT imaging) was described by Zhang et al. [63-65]. For both in vitro and in vivo studies, results demonstrated that the nanoprobe has a favourable practicality with strong biocompatibility, exceptional tumor-targeting ability, and long blood circulation half-life.

3. Conclusions

Au NPs for medication delivery, imaging, and biodiagnosis have garnered a lot of attention and research, as shown in this review. Toxicology, imaging, noninvasive disease detection and therapeutic delivery are all made easier by their small size, low intrinsic toxicity, high surface area and ability to quickly functionalize with biomolecules. Constructing multifunctional Au NPs through the conjugation of multiple targeting ligands is needed in future research. For optimal therapeutic combinations, the Au NP formulations must be fine-tuned and customised.

Developing a method for making the theoretically expected nanostructure from Au NPs is also necessary, as is creating a model for the NPs with the needed attributes. Last but not least, the long-term cytotoxic and genotoxic effects of Au nanostructures, as well as their efficacy as a target in vivo and in vitro, should be investigated.

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