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Metal-based nanosystems for diagnosis

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Abstract

The impressive diversity related to etiologic factors and the distinctive genetic and immunological behavior attained by various conditions represent the fundamental reasons for high-rated inefficient and eventual hazardous strategies entailed by conventional healthcare practice. Thanks to the tremendous progress reported in nanotechnology during the last decades, various unconventional and promising strategies have been successfully developed and examined with respect to potential genuine biomedical applications. Given the amazing possibility to manipulate matter at a molecular and atomic level and the incessant need to design and implement personalized therapies, various nanosized systems have thus been engineered. Among the newly developed nanomaterials, metallic nanoparticles have gain attention during the intense biomedical research activity, thanks to their peculiar size-conditioned properties. An efficient therapeutic strategy begins with an accurate diagnosis result, so the immediate requirement of such specific detection tools is conspicuous. The use of silver and gold in day-to-day activities is acknowledged since ancient times, but the novel technological opportunities extended their particular applications towards personalized medicine. It is worthy to mention that the unexpected nanodimension-related features of the aforementioned noble metals strongly recommend them for a large number of current applications in nanomedicine, including novel and specific metallic nanostructures used in diagnostics.

Keywords: nanotechnology, silver nanoparticles, gold nanoparticles, molecular biosensing, biomedical imaging.

Introduction

The current medical healthcare system still reports alarming inefficiency and side effects in conventional therapies, but in the light of new emerging pathologies, because of human genetic complexity, there is an obvious necessity to develop new systems that provide accurate diagnosis and personalized treatment tools for patients.

According to the currently available etiologic, epidemiologic and therapeutic data on specific microbial infections, the alarming phenomenon regarding the development and enhancement of conventional therapy resistance is well known due to the actual difficulty encountered in the accurate detection and treatment of such pathologies [1–3]. For this reason, research recently turned its attention towards the development and clinical use of peculiar designed structures that provide targeted diagnosis and treatment for infectious diseases. Likewise, the impressive structural, genetic and behavioral diversity found in various types of cancer cells alerted the world medical community in such a way that the current medical research is targeted towards the detection of biological molecular markers that provide specific tumor diagnosis [4–8]. Furthermore, the limited efficiency and potential side effects reported in conventional antitumor treatment – radiotherapy, chemotherapy and surgery [9–12] – encouraged the development of novel specific molecular systems that provide accurate diagnosis and proper therapy for tumor structures [1, 13, 14]. By also considering the genetic and immunological versatility underlying degenerative pathologies [15–17] and genetic disorders [18–21], there is a large interest in early diagnosis methods for such diseases, in order to provide feasible treatment strategies.

Considering the principles of life science, material engineering, regenerative medicine and modern healthcare practice, the recently reported nanotechnologies made remarkable progress in various fields, including medicine [1, 14]. Given the versatile synthesis methods of this novel and powerful trend – which allows molecular and atomic manipulation of matter and a wide applicability for a large number of materials from various domains [22, 23] – there are already reports of some specific potential applications for nanotechnologies in the biomedical field, such as targeted and controlled drug delivery systems [24–26], biomedical imaging [27–29], gene therapy [28, 30, 31] and antitumor therapy [29, 32, 33], tissue engineering [34, 35]. Although the goal of a personalized therapy still represents a challenge for the medical and scientific world, the productive convergence of nanotechnology and medical research enables tremendous possibilities to engineer novel organic or inorganic, natural or synthetic, composite or hybrid systems, which represent excellent candidates for individual medical healthcare strategies [24, 26, 28, 32, 34].

Thanks to their specific physical and chemical properties, metallic materials seem to be ideal targets for nanotechnologies, in order to develop new low-dimensional systems for biomedical applications. The available *bottom-up* (starting from bulk materials) and *top-down* (starting from molecular and atomic structures) synthesis methods offer unlimited possibilities to engineer nanosized metal-based systems, which exhibit unique structural,

morphological and functional properties due to their specific high surface/volume ratio [22, 29, 36, 37]. The tremendous versatility in fabricating low-dimensional systems (including physical, chemical, biological and biomimetic approaches) provides the opportunity to create various metallic particles, with nanoscale dimensions (2–100 nm) and different morphologies (sphere, cube, polyhedron, triangle, hexagon, polygon, plate, rod, wire, ribbon, inflorescence), distinguished by peculiar dimension-subjected properties [37–39]. The dimensional and morphological features of metallic nanodevices enable proper interaction with physiological and pathological structures, while specific physical and chemical properties provide unlimited functionalization possibilities (by using various natural or synthetic and simple or complex structures, such as metallic or ceramic coatings, polymeric molecules, amino acids, peptides, proteins, enzymes, polysaccharides, nucleic acids, antibodies), all in order to minimize potential side effects and to encourage the development of novel nanosized metal-based functional structures [29, 38–40].

All the specific properties of metallic nanostructures strongly recommend them to be used in various biomedical applications, including the development of metal-based tools for diagnosis. Therefore, we propose in the following paragraphs an overview of the latest metallic nanosystems, engineered and assigned for the benefit of novel medical diagnosis strategies.

Silver nanoparticles (AgNPs)

As a result of its historically acknowledged biocide activity, silver has been used in manifold day-to-day activities and unconventional medical practices for a long time [41–43]. The immediate demand of modern world regarding novel materials and improved medical devices along with the tremendous improvement of nanotechnologies, led to genuine engineered silver-based materials, which are currently intensely investigated regarding their antibacterial [44–48], antifungal [42, 48, 49], antiviral [42, 50, 51], anti-inflammatory [24, 42, 52, 53] and antitumor [42, 51, 54, 55] effect. As we propose to point out in the subsequent paragraphs, various nanotechnology-based synthesis methods were successfully applied to design silver nanostructures, distinguished by a wide variety of dimensional and morphological features.

Obtaining methods

The impressive progress in matter manipulation led to the development of various synthesis methods for silver-based nanomaterials, which are specifically classified by their physical and chemical fundamentals. Thus, the current process in obtaining low-dimensional structures of the aforementioned noble metal employs distinctive synthetic approaches – such as physical, chemical and biological – whose features will be revealed in the following paragraphs.

During the physical method processes, AgNPs can be easily synthesized by considering the evaporation-condensation phenomena of bulk silver [44, 56]. Various external energies encourage the formation of metal species inside different inert atmospheres of the experimental equipment's working enclosures, which are subsequently carried to suitable substrates [57, 58]. Thus, several physical methods have been successfully used in experimental research studies to produce high purity nanosized silver particles, with preferential distinctive sphere-like morphology, uniform and reduced size distribution, such as thermal plasma [59–63], radiofrequency sputtering [64–67], arc discharge [68–71], ion implantation [72–74], pyrolysis [75–77], laser ablation [78–82].

The chemical route for AgNPs synthesis involves electrochemical and controlled degradation processes of the organometallic precursors (silver metallic salts), in order to produce colloidal suspensions that are stable in aqueous or organic solvents [83, 84]. The proper adjustment of reaction parameters – such as temperature, pH, reagent concentration, reducing agent and stabilizer – enables the facile manipulation of nucleation, incubation and maturation processes involved in particle formation, in order to manufacture high purity and with controllable size and shape AgNPs [44, 56, 84]. Promising results have been reported regarding silver nanosized particle synthesis by using various inorganic (sodium borohydride [84–86], hydrazine [86–88], dimethylformamide [88, 89]) and organic (amines [88, 89], aldehyde [90], polysaccharides [91–93], peptides and proteins [88, 89, 94], alcohols [95, 96]) reducing agents, but also by using various stabilizers such as carboxylic acids [97, 98] and amino acids [99], amines [95, 100], polymers [86, 101], ionic or non-ionic surfactants [102–104] and dendrimers [105, 106]. Successful results regarding AgNPs synthesis in liquid phase have also been reported by several experimental studies that used different external energy sources during the chemical formation processes. Thus, various morphologies of silver nanosized particles were acquired by using ultrasound [107–109] and electromagnetic (UV light [110, 111], VIS light [112, 113], γ radiation [98, 114, 115], microwave [90, 103, 116]) irradiation synthesis.

In order to overcome the main drawbacks of physical (expensive acquisition and further maintenance of the equipment) and chemical (biological and environmental risk) synthetic approaches, the researchers tested and promoted the biological route for AgNPs synthesis [43, 117, 118]. The novel trend of *bottom-up* biosynthesis permits the fabrication of homogenous and controllable shape and dimension particles, by suitable revaluation of the reducing and antioxidant properties of plant extracts and by the proper use of bioreduction mechanisms common in various microorganisms [43, 50, 119]. Considering the dual activity (reducing and stabilizer agent) of specific phytochemicals procured from vegetal organisms, exciting results have been reported through the use of plant extracts from pepper [120, 121], garlic [122, 123], basil [119, 124, 125], camphor tree [118, 126], blueberry [127, 128], blackberry [128], coconut [129, 130], banana [131, 132]. Also, AgNPs biological manufacture was successfully performed by using extracellular synthesis of various bacterial strains (*Escherichia coli* [133, 134], *Klebsiella pneumoniae* [135, 136], *Pseudomonas aeruginosa* [137] and *Staphylococcus aureus* [134, 138]) and fungal strains (*Aspergillus* spp. [139, 140], *Candida* spp. [141, 142], *Cladosporium* spp. [134], *Fusarium* spp. [126, 143], *Penicillium* spp. [144], *Trichoderma* spp. [145, 146]).

Each of the aforementioned synthesis paths may own

its peculiar advantages and disadvantages, but considering the final application of silver nanostructures, the physical and chemical versatility of bulk silver and silver-based compounds, and also the tremendous progress recently reported in technology, there is an impressive diversity in experimentally synthesizing AgNPs of controllable size and morphology.

The efficiency of silver-based nanosized structures designed for medical diagnosis applications significantly depends on AgNPs properties, such as dimension, shape, particle distribution, surface physics and chemistry, optical properties. As it will be revealed in the following paragraphs, the unique features of silver nanoparticles have been intensively explored, in order to develop novel silver-based nanosystems for diagnosis.

Molecular biosensing

Specific detection of various disorders still represents a real challenge in modern diagnosis and is the main drive for researchers to develop novel reusable, personalized and sensitive pathological detection tools. Considering the discreet properties of silver at the nanoscale, new-engineered systems based on AgNPs proved to fulfill the optimal requirements for biological molecular sensors.

A recent experimental study performed by Ren *et al.* [147] exposed the possibility to produce novel sensors based on silver nanoparticles self-assembled into diatom frustules, for improved specificity and sensitivity of surface-enhanced Raman spectroscopy (SERS) sensors. Synthetic silica was produced from *Pinnularia* spp. marine microorganisms by biomimetic mechanisms and subsequently immersed into a colloidal suspension of silver particles with nanometric dimensions (50–150 nm), produced by a facile chemical route (by using boiling reaction of $AgNO_3$ aqueous solution and sodium citrate). Rhodamine 6G dye was examined in resonance and non-resonance conditions by using both the experimental manufactured sensors and the conventional sensors (consisting of AgNPs on glass). The experimental data related to the proposed AgNPs-based sensors showed 4–6 times (for resonance conditions) and 9–12 times (for non-resonance conditions) improved sensitivity to detect the dye, results which significantly increase the enhancement factor of SERS sensors. According to the authors, the experimental structures can further be used to produce more accurate sensors for molecular physiological and pathological detection.

The impressive properties exhibited by silver nanoparticles in optically active substrates give rise to opportunities for novel molecular sensing tools, a hallmark of other research studies. Thus, specific aligned and high sensitivity thin layers based on silver nanowires with 80–100 nm diameter and 1.6–2 μm length were successfully formed on the inner surface of glass capillaries, in order to produce portable, reusable and durable substrates for molecular SERS sensors [148]. Also, AgNPs-based plasmon-active substrates for molecular detection devices were successfully produced by chemical synthesis [149–151], soft lithography [152], electron lithography [153] and pulsed laser ablation [154]. Specific detection of microbial membrane molecules may be feasible thanks to the promising plasmonic properties attributed to silver nanocubes coated with silica [155] or polymer [156], that provides suitable platforms for microorganism sensing assays.

The research study performed by Karabchevsky *et al.* [157] reports the nano-silver structural modification of glass electrodes, in order to produce sensitive sensors for reduced concentrations of endocrine hormones, such as estrone. By using evaporative deposition of bulk silver, a thin layer of silver (47 nm) was deposited on the glass substrate. Furthermore, 11-mercaptoundecanoic acid (11-MUA) was used to protect the silver nanolayer and *N*,*N*'-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) were used to encourage reactive silver surfaces, in order to specifically immobilize rabbit anti-estrone IgG antibodies. The experimental luminescence results showed successful immobilization of the specific immunoglobulin on thin silver nanolayers. The sensitivity assays based on surface plasmon resonance (SPR) technique against female synthetic estrone solution revealed a continuous increase of the SPR angle, depending on the hormone concentrations, which proved the specific sensing of the designed silver-based sensors.

The successful use of triangular AgNPs to produce sensitive nanosensors for p53 protein (specific molecular structure involves in head and neck squamous cell carcinoma) was reported by Zhou *et al.* [158]. By using a thermal evaporation process, a 50 nm layer of silver was deposited onto the glass substrates that have been previously spin-coated with commercially nanosphere solution. The further sonication enabled the removal of the nanospheres and the formation of AgNPs, thus obtaining a triangle-like silver nanoarray (120 nm in-plane widths and 40 nm out-of-plane heights) by nanosphere litography. 11-MUA and 1-octanethiol (1-OT) were used to produce a self-assembled protective monolayer, while 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and sulfo-*N*-hydroxysuccinimide (S-NHS) were used to encourage the binding of specific monoclonal mouse p53 antibodies. The localized surface plasmon resonance (LSPR) performed *in vitro* against human serum samples showed a significant peak shift for cancer-sick patients, compared to healthy patients. Thus, this study promotes a novel AgNPs-based LSPR biosensor for sensitive detection of human p53 tumor protein.

A research study regarding the tremendous opportunity to develop new chemotherapeutics by developing novel sensing tools to evaluate the interactions between p53 protein and mouse double minute protein (MDM2) was performed by Robson *et al.* [159]. Their experimental activity considered the specific synthesis of 40 nm AgNPs reduced by ethylenediaminetetraacetic acid (EDTA), and further conjugation with 12.1 peptides (part of p53 mimics peptides with high affinity for MDM2 hydrophobic *N*-terminal) previously modified with benzotriazole (BT) dyes. The SERS results showed a specific dependence of the signal intensity on MDM2 concentration, while the SERS, dynamic light scattering (DLS) and extinction spectroscopy data were successfully used to investigate the allosteric interactions between MDM2 and AgNPs-based system, in order to further produce potential antitumor drugs.

Considering the cumulative attractive properties of multi-walled carbon nanotubes (MWCNTs) and silver (Ag) and gold (Au) nanoparticles, Zhang *et al.* [160] recently

developed a promising biosensing device based on a carbon electrode modified with ~25 nm spherical Au–Ag alloy NPs coated onto MWCNTs surface, for gastric cancer specific volatile metabolites. The specific sensitive activity of the designed sensor was assessed during *in vitro* tests against human gastric cancer cell line (MGC-803) and healthy human gastric epithelial mucosa (GES-1), and the subsequent evaluation of cell culture supernatants by mixed HS-SPME/GC-MS (headspace solid-phase microextraction/gas chromatography-mass spectroscopy) analytical method. The experimental results showed significant levels of alcohols and aldehydes in the tumor cell media, due to the intense enzymatic activity of aldehyde dehydrogenase in MGC-803 cancer cells. The potential application of such biosensor for gastric cancer early detection was also confirmed after electrochemical measurements, which showed specific activity in MGC-803 tumor cells detection.

In order to provide a specific detection of trypsin (digestive enzyme produced by pancreatic acinar cells) Hong *et al.* [161] designed a free-label biosensing assay by using silver nanoclusters (AgNCs) and cytochrome c (cyt c). First, spherical silver nanoclusters with 2 nm average size, high negative electric charge and high fluorescent emission were produce by using DNA oligonucleotide as a template. To create the specific sensing structure for trypsin, a hybrid complex consisting of AgNCs and positively charged cyt c was further produced, and the analytical experimental data showed a strong inhibition effect of the metalloprotein against oligonucleotide-templated AgNCs fluorescence spectra. By adding trypsin solution to the hybrid silver-based nanosystem, a specific cyt c hydrolysis occurs and the fluorescent emission of AgNCs is significantly restored depending on enzyme amount. Considering the reported results of the study, a novel nanosilver-based sensing system was designed for specific detection of exocrine pancreas enzymatic disorders.

Specific diagnosis of glucose disorders is a current concern for the medical world and this troubling situation lately led to the development of several silver-based sensors [162–164]. By using an electrochemical synthesis method, Ma *et al.* [165] successfully produced a novel sensing device based on indium tin oxide (ITO) conductive glass, dendritic silver nanoparticles with diameters ranging from 70 nm to 280 nm, 50–100 nm thickness dielectric polyvinyl alcohol (PVA) layer and high purity silver slice. The experimental UV–VIS absorption spectra of the designed system against various glucose aqueous solutions showed distinctive absorption peaks with specific slight red shifts, depending on the various refractive indexes of glucose concentration solutions. Furthermore, the researchers showed easy removal of the glucose solution from the sensor's surface and significant color modification thanks to the red shift phenomena, which significantly converts the device into a long-term reusable sensor for the naked eye observation of glucose levels.

Considering the impressive diversity of pathogenic molecular structures and the current concerning phenomenon of low specific and non-sensitive diagnosis tools, there is an immediate demand to develop improved and more accurate detection systems. Thanks to their attractive plasmonic properties, specific surface chemical versatility and high affinity for negative charged pathogenic and non-pathogenic structures, AgNPs proved to be the optimal candidates for novel molecular detection devices, thus being used in specific detection of various pathogenic functional groups or molecules, such as amino acids [166, 167], proteins [168, 169], enzymes [159, 170], antibodies [171, 172], nucleic acids [149, 173–175] and saccharides [161–163].

Biomedical imaging

The optical features of silver nanoparticles – strongly affected by dimension and morphology [43, 53] – enabled their successful use in promoting novel AgNPs-based tools for biomedical imaging. The development of such diagnostic devices often involves specific binding of conventional imaging agents and requires specific identification of pathological molecular structures and proper revaluation of silver nanoscale features (optical and electrical properties, chemical reactivity, dynamic behavior, anti-inflammatory and antimicrobial effects). As it will be revealed in the following paragraphs, various silver-based systems have been engineered and evaluated for medical imaging diagnostic applications.

A silver-based plasmonic tool for specific imaging of cellular internalization studies was recently developed by Braun *et al.* [176]. Spherical silver nanosized particles were coated with specific C-terminal peptides conjugated into a NeutrAvidin (NA) shell and further covered with fluorescent green CF488 dye-labeled polyethylene glycol (PEG). In order to provide specific imaging for intracellular AgNPs, a silver etching solution consisting in hexacyanoferrate (HCF) and thiosulfate (TS) was used during the *in vitro* assays, which were evaluated against human prostatic cancer PPC-1 cell line. According to the authors, the HCF-TS redox mixture enabled the non-toxic and fast dissolution of extracellular AgNPs, while the intracellular metal nanoparticles were protected by cellular substances. Thus, the fluorescence microscopy showed specific yellow high fluorescent images for the particles inside the culture cells, while the dark field microscopy evaluations showed characteristic red-shifted AgNPs clusters near cell's nuclei. Furthermore, the toxicity of AgNPs and etching solution was evaluated by *in vivo* assays performed against albino mice and the reported results showed normal hepatic enzymes and renal metabolites, specific to a non-pathological activity. The experimentally designed nanodevice revealed significant results for specific tumor cell detection, while the NA-conjugated peptides exhibit ideal binding sites for antitumor drugs, in order to build a novel AgNPs-based nanosystem for cancer specific detection and treatment.

An attractive approach to produce AgNPs-based tumor imaging systems was performed by Gao *et al.* [177]. Due to their intense proliferative activity, cancerous cells exhibit significant higher concentrations of glutathione (GSH) and oxidized glutathione disulfide (GSSG), compared to healthy eukaryote cells. Considering this condition, the authors of this research study evaluated *in situ* obtaining of self-imaging silver nanoclusters by spontaneous biosynthesis mechanism of $[Ag(GHS)]^+$ silver salt incubated within human liver hepatocellular carcinoma HepG2, human lung adenocarcinoma A549 and human

cervix adenocarcinoma HeLa cell lines. Specific sphere morphology and uniform dimension (1.1±0.2 nm) particles were thus synthesized, and the *in vitro* cytotoxicity assay performed against HeLa cell cultures and human healthy embryo liver (L02) cell cultures showed significant tumor cell death after 72 h of incubation, compared to more than 80% healthy cell viability. Confocal fluorescence microscopy was used to examine the *in vitro* imaging assays, performed on cancerous and healthy cell lines in $[Ag(GHS)]^+$ and high glucose (control) media. The 24 h reported data showed significant NIR fluorescence signals for HepG2, A549 and HeLa cells, compared to the drastically reduced signal assigned to L02 cell cultures. Also, to fortify the *in vitro* promising results, nude mice with cervical carcinoma xenografted tumors were intravenously or local inoculated with silver salt solutions to evaluate the *in vivo* potential tumor diagnosis, up to 14 days. According to the reported data, specific NIR fluorescence images were collected for cancerous tissues and the histological *ex vivo* examination showed normal vital organ tissues.

Another study – performed by Mukherjee *et al.* [178] – reveals the possibility to produce a novel silver-based tool for diagnostic imaging by using biosynthesized AgNPs, obtained thanks to the specific reducing and capping activities of *Olax scandens* (subspecies of *Oleaceae* family) leaf extract against $AgNO_3$ salts. Considering the presence of specific phytochemicals with significant fluorescence properties from the methanolic leaf extract, the biological obtained spherical AgNPs (20–60 nm) could easily be investigated for their bioimaging potential. In order to evaluate the cytotoxic effects and imaging ability of AgNPs against cancerous cells, *in vitro* assays were performed against A549 and mouse melanoma (B16) cell lines. The MTT cytotoxicity assays revealed significant anti-proliferative activities of AgNPs against tumor cell cultures, while the fluorescence microscopy showed specific red fluorescent images for both A549 and B16 cells.

Xia *et al.* [179] reported the successful use of spherical AgNP dimers coated with silica for cancerous cells imaging. By using CF_3COOAg and ethylene glycol, 60 nm silver nanocubes were obtained at first, that were further suspended in dispersed polyvinylpyrrolidone (PVP) – ethanol mixture and treated with $Fe(NO_3)_3$ aqueous solution, in order to produce 50 nm silver nanosphere dimers. The subsequent functionalization of the synthesized AgNPs was performed by using 4-mercaptobenzoic acid (4-MBA), silica shell and specific conjugation of human epidermal growth factor receptor 2 antibodies (anti-HER2). The imaging potential of the AgNPs was evaluated during *in vitro* assays, that were performed against previously fluorescein isothiocyanate SERS-labeled human breast adenocarcinoma SK-BR-3 (that overexpress HER2 gene product) and human glioblastoma astrocytoma U-87 MG (as negative control) cell lines. The silver nanodimers showed specific SERS signal for SK-BR-3 cell cultures, compared to the lack of SERS activity in U-87 MG cells. Also, the silver-based dimer revealed the strongest SERS signal during *in vitro* SK-BR-3 cells evaluation, compared to conventional 60 nm silver nanocubes and 50 nm silver nanospheres, which give the possibility to use the AgNP dimers in further SERS imaging for early breast cancer detection.

Various specific features of AgNPs were revaluated by Zou *et al.* [180] during their research study regarding micro-computer tomography (CT) imaging of silver nanoparticles used for *in vivo* treatment of chronic otitis media against rats. 117±24 nm polyhedral silver particles coated with PVP stabilizer were dispersed and trans-tympanic injected to the animal models. The microCT images showed AgNPs dynamic motion towards inner ear, by specific crossing of round and oval windows and large ability to access various regions of the ear (depending on the AgNPs dosage). The microbial properties of silver nanoparticles strongly recommend their as chronic otitis therapeutic agent, while the optical and surface chemistry features of this structures enable the suitable development of targeted drug delivery systems with specific microCT imaging of the dynamic healing process.

A promising streptavidin-conjugated aptamer-functionalized AgNPs system designed for intracellular protein imaging was performed by Chen *et al.* [181]. The potential use of the AgNPs as imaging agents for future diagnostic applications was evaluated by *in vitro* assays, which showed significant enhanced fluorescent signals for the silver-based detection tools during dark field microscopy and transmission electron microscopy examinations. A similar experimental nanosystem – based on AgNP core, gold (Au) shell and aptamer functional layer – was developed by Hu *et al.* [182] and it was successfully *in vitro* evaluated for specific and sensitive detection and imaging of platelet-derived growth factor-BB protein.

Thanks to their peculiar properties, AgNPs represent an attractive source for new and improved medical imaging techniques. The potential use of silver nanosized structures for various tumor tissue imaging is the most explored application, due to the current non-specific diagnostic tools and thanks to the considerable progress of immunohistochemistry. It is important to note that various silver-based detection devices were recently developed to enable specific and sensitive bioimaging of severe non-cancerous disorders, such as neurodegenerative disorders [183, 184] and cardiovascular disorders [185, 186].

Gold nanoparticles (AuNPs)

Lately, gold nanoparticles (AuNPs) have been intensively used in biomedical applications like: (1) vaccines [187, 188]; (2) transfection [189, 190]; (3) cancer therapy by photothermal activation and/or drug delivery [191–195]; (4) biomedical sensors [196–198]; (5) imaging diagnostics [199–201]; (6) cosmetics [202]; etc. This reason interest in AuNPs for medical purposes is given by their properties: (1) photoactivation capability; (2) inert character; (3) biocompatibility; (4) easily and high yield obtaining methods; etc.

One important property of gold nanoparticles is given by their capability of photoactivation by means of surface plasmon resonance, manifested by the rise of absorption band in VIS, because the free electrons in the conduction band suffer a collective resonant oscillation when the metal is irradiated with an incident light [203].

Obtaining methods

There are several approaches for AuNPs obtaining, which can be classified as chemical, electrochemical or

physical methods. In the first category, we recall the (1) citrate reduction [204], (2) the Brust–Schiffrin method [205], (3) the sodium borohydride reduction [206], as the most encountered methods for gold nanoparticle synthesis. Nowadays, the reduction of Au salts is done in very different non-toxic reducing media and even in living organisms, which have the ability to produce metal ions. This approach is referred to as green synthesis of nanoparticles, which offers some advantages like: (1) no harmful impact of the environment; (2) high yield synthesis; (3) homogeneity in size and morphology of the resulted gold nanoparticles; (4) higher biocompatibility.

The electrochemical approach is used to obtain highly biocompatible gold nanoparticles in electrode cells, by oxidizing the anode to produce metal ions, which are further reduced on the surface of the cathode. Surfactants can be used in order to control the size and dispersion of the resulted particles.

Regarding the physical methods used for AuNPs obtaining, we can name the γ-irradiation method [207], UV irradiation [208], or microwave irradiation [209]. Despite of their denomination, these methods are actually a combination of physical and chemical methods, as they suppose the use of Au salts as precursors and weak reducing agents, the reaction being triggered by giving an external energy to the system (Tables 1 and 2).

Table 1 – ***Classical obtaining methods for gold nanoparticles (AuNPs)***

Class	Method	System description	Applications	References
Chemical	Citrate reduction	$HAuCl_4 \cdot nH_2O$ reduced in trisodium citrate, at boiling point	Highly functional nanoparticles	[210, 211]
		$KAuCl_4$ reduced in trisodium citrate at 75^0C	–	[212]
	Sodium borohydride reduction	$HAuCl_4$ reduced in sodium borohydride and water/toluene; thiol capping agent; pegylated-poly(DL-lactic-*co*-glycolic acid) nanospheres encapsulation and methotrexate loading	Rheumatoid arthritis diagnostic and treatment	[213]
		$HAuCl_4$ reduced by tryptophan and sodium borohydride	Deep UV imaging of microbial cells	[214]
Electrochemical	Deposition	Deposition on indium tin oxide glass	Biosensors	[215]
		Deposition on graphite rod	Glucose biosensing	[216]
Physico-chemical	γ-Irradiation method	$HAuCl_4 \cdot 3H_2O$ G5-NH_2 PMAM dendrimers under γ-irradiation (75 Gy/min., 125 min.)	–	[217]
		$HAuCl_4 \cdot 3H_2O$ reduction in sodium alginate under 8 kGy γ-irradiation	–	[218]
	UV irradiation	$HAuCl_4$ reduction in poly(vinyl pyrrolidone), poly(vinyl alcohol) and citric acid, under UV irradiation	–	[219]
	Microwave irradiation	$HAuCl_4$ reduced in *Cissus quadrangularis* extract, *via* microwave irradiation	–	[220]
	Electrospray-assisted chemical reduction	Electrosprayed aerosol of $HAuCl_4$ into a octadecyl-aminomethanol and cyclohexane bath	Electronic applications	[221]
Physical	Laser ablation	Nd:YAG laser, double-pulse mode, 1064 nm	–	[222]
		Nd:YAG laser, 1064 nm, in deionized water and aqueous chitosan solutions	–	[223]
	Plasma synthesis	Atmospheric plasma synthesis using $HAuCl_4$, chitosan and *N*-tert-butyl-α-phenylnitrone	–	[224]
	UV irradiation	$HAuCl_4$ reduction by UV irradiation, with no additional substances	–	[225]

Table 2 – ***Green methods for gold nanoparticles (AuNPs) obtaining***

Method type	System description	Function	Evaluation	References
Plant extract reduction	*Pleurotus florida* glucan reduced $HAuCl_4$	Catalytic activity	Reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP), in the presence of sodium borohydride	[226]
	Commelina nudiflora extract reduced tetrachloroaurate salt	Antibacterial and antioxidant activity	*In vitro* anti-bacterial activity against *E. coli*, *S. aureus*, *E. faecalis*, *S. typhi*; *in vitro* DPPH and ABTS antioxidant assays	[227]
	α-NADPH-dependent sulfite reductase purified from *Escherichia coli*	Antifungal activity	*In vitro* antifungal activity; *in vitro* biocompatibility for Vero and Hep-2 cells	[228]
Living organisms production	Intracellular synthesis using *Tetraselmis kochinensis* alga	–	–	[229]
	Aspergillus fumigatus intracellular synthesis	–	–	[230]

Molecular biosensors

A biosensor is a device capable of analytical detection, based on combining a biological component with a physico-chemical detector. It is composed of: (1) a biological element/biologically derived/biomimetic component, which recognizes the targeted analyte; (2) a transducer, which converts the interaction signal in other type of signal (voltage); (3) the electronic system analyzing the received signal [203].

The growing interest for AuNPs in molecular biosensors is given by the special properties offered by these nanoparticles, such as: (1) optical properties; (2) conductivity; (3) catalytic properties; (4) high surface-to-volume ratio; (5) high density; (6) high surface energy, hence reactivity. The most important property of gold nanoparticles, which makes them useful in such sensing applications, is given by the surface plasmon resonance and the ability of AuNPs to transfer electrons in a fast and

direct manner from electroactive species to the electrodes. Moreover, these particles have the ability to assure signal amplification, due to the light-scattering properties and local electromagnetic field enhancement capability [203].

The resulted molecular biosensor must provide the following properties: (1) high sensitivity; (2) fast response; (3) high selectivity; (4) sigh stability; (5) low implementation cost [203] (Table 3).

Table 3 – ***Examples of gold nanoparticles (AuNPs)-based molecular biosensors***

Type	System description	Application	Evaluation	Reference
Electrochemical	Molecularly imprinted polymer membrane–glassy carbon electrode–multi-walled carbon nanotubes–AuNPs	Cholesterol detection	Cyclic voltammetry, differential pulse voltammetry; linear response 1×10^{-13} and 1×10^{-9} mol L^{-1}, limit of detection 3.3×10^{-14} mol L^{-1}	[231]
	Fe@AuNPs–2-aminoethanethiol-carbon nanotubes–modified glassy carbon electrode obtained in cyclic voltammetry in presence of pyrrole	Cefexime detection	Detection limit 1.0×10^{-10}–1.0×10^{-8} M and 2.2×10^{-11} M	[232]
	AuNPs/toluidine blue–grapheme oxide modified electrode	Multidrug resistance gene detection	Decreased currents proportional to the logarithm of DNA concentration in differential pulse voltammetry in the range 1.0×10^{-11}–1.0×10^{-9} M with a detection limit of 2.95×10^{-12} M (at an S/N of 3).	[233]
	SBA-*N*-propylpipyrazine-*N*-(2-mercaptopropane-1-one) mesoporous–AuNPs–screen-printed graphite electrode	G-quadruplex (G_4) DNA–drug interaction	Cyclic voltammetry interaction of Cephalexin with G_4DNA	[234]
	AuNPs–multiwalled carbon nanotubes–Au electrode	Single-stranded (ss) DNA hybridization biosensor	Cyclic voltammetry measurements of ssDNA hybridization assessed by the reduction peak current of methylene blue; the concentration range 1.0×10^{-15}–1.0×10^{-8} M with the detection limit 3.3×10^{-16} M (3σ); detection of 10 CFU $mL^{-1}$of *S. aureus* in the tap water	[235]
	DNA capture probe–graphene/Au nanorod/polythionine–glassy carbon electrode	Human papillomavirus detection	Electrochemical impedance spectroscopy and differential pulse voltammetry using $[Ru(phen)_3]^{2+}$ as redox indicator for the coupling reaction of target DNA to capture DNA; range of detection of 1.0×10^{-13} to 1.0×10^{-10} mol/L with a detection limit of 4.03×10^{-14} mol/L	[236]
Optical	AuNPs assembled film–polyelectrolyte multilayer modified sidewall of unclad optical fiber	Immunosensor	Capability to detect the bulk phase refractive index changes and antibodies assays; the sensitivities are 13.09 AU/RIU (R=0.9678) for 48-nm Au and 5.85 AU/RIU (R=0.9666)	[237]
	AuNPs–cylindrical nanofibers of poly(vinylidene fluoride)	High-sensitivity for the label-free sensing of biomaterials	Polarized UV–VIS extinction spectroscopy showing improved refractive index sensitivity (over 500 nm/RI unit maximum)	[238]
	AuNPs/6-mercaptohexan-1-ol/ gelatin	Optical biosensing platform for a proteinase activity assay	Proteinase digestion of gelatin increases the interactions between AuNPs, which aggregate determining a red shift visible with naked eye	[239]
Piezoelectric	Quartz crystal microbalance (QCM)–gold nanoparticles–secondary antibodies goat anti-mouse IgG	Immunodetection of small molecules	Linear relationship with 2,4-D concentrations in the range of 13.3–666.7 ng/mL; detection limit at about 13.0 ng/mL	[240]
	Thiolated single-stranded (ss) DNA–AuNPs–thiolated Au electrode-quartz crystal microbalance	*E. coli* O157:H7 detection	Hybridization determines a mass change; cyclic voltammetry and electrochemical impedance spectroscopy; 1.2×10^2 colony forming unit (CFU)/mL *E. coli* O157:H7 cells can be detected	[241]

Biomedical imaging

Gold nanoparticles have been already approved by *Food and Drug Administration* to be used in biomedical applications. One example is NanospectraAuroShell particles [242] with applications in the photothermal ablation of solid tumors and potential use as contrast agent in different medical imaging techniques, like optical coherence tomography, photoacoustic tomography, radiolabeling, narrowband imaging, enhanced fluorescence and two-photon luminescence.

AuNPs can be used in various biomedical imaging techniques, such as optical (photoacoustic [243–245], surface enhanced Raman spectroscopy SERS [246, 247], X-ray imaging [248–252], single-photon emission computed tomography SPECT and positron emission tomography PET [253].

The applications of gold nanoparticles in optical imaging techniques is determined by its absorption capability and scattering properties, while in X-ray and MRI, besides of the high absorption, the high density is also implied. The high tissue permeability of AuNPs makes them useful in SPECT and PET imaging, when labeled with different radioisotopes. However, a recent trend in developing gold nanoparticle-based contrast agents consists in obtaining multimodal imaging systems,

suitable for more than two techniques; these materials are usually multifunctional platforms, offering a facility for both diagnosis and therapy (by means of photothermal ablation of tumor cells) (Table 4).

Table 4 – ***Examples of gold nanoparticles (AuNPs)-based systems for biomedical imaging***

Imaging technique	System description	Application	Evaluation	Reference
Fluorescence imaging	Red dye–AuNPs–DSPE–poly ethylene glycol	Targeted imaging of tumors using fluorescence SPECT/CT	*In vivo* imaging for tumor bearing BALB/c mice	[199]
Computer tomography (CT)	Acetylated dendrimer–AuNPs	CT imaging of cancer cells	*In vitro* and *in vivo* imaging for human lung adenocarcinoma cells	[254]
	PEG–dendrimer–AuNPs	CT imaging for cancer diagnosis	Long half-time proved in pharmacokinetic studies; *in vivo* blood pool imaging in intravenously injected mice and rats; *in vivo* imaging of tumor bearing mice	[255]
	Folic acid–dendrimer–AuNPs–Gd	Targeted imaging of tumors using CT/MR	High X-ray attenuation intensity and reasonable r_1 relaxivity; *in vitro* xenograft tumor model; *in vivo* imaging for tumor inoculated BALB/c nude mice	[256]
	Hollow AuNPs–doxorubicin	Radiosensibility improvement and CT imaging of tumor xenograft	*In vivo* tumor growth delaying and weight reducing; *in vivo* imaging in tumor bearing mice	[200]
Photoacoustic	Prussian blue@AuNPs	Cancer diagnosis and guidance for photothermal therapy	*In vivo* imaging of tumor bearing mice and complete photothermal ablation with no recurrence	[257]
Magnetic resonance imaging (MRI)	Fe_2O_3/AuNPs/thiol-PEG-carboxyl/anti-CD105 antibodies	MR imaging of tumor angiogenesis	*In vitro* labeling of human umbilical vein endothelial cells; *in vivo* imaging for breast cancer tumor bearing mice; resected xenografts for immunohistochemistry staining and tumor microvessel density measuring	[258]
	Gd–dendrimer–AuNPs	MR/CT imaging	*In vivo* biodistribution studies showing extended blood circulation time, 24 h clearance	[259]
	Fe_3O_4@Au–polyethyleneimine–hyaluronic acid	Targeted multifunctional platform used in MR/CT/thermal imaging and photothermal therapy of tumors	*In vitro* imaging for tumor xenograft model; *in vivo* imaging on HeLa tumor bearing BALB/c nude mice; *in vitro* and *in vivo* photothermal ablation of tumor cells; *in vivo* photothermal imaging	[260]
Ultrasound	Mesoporous silica nanocapsule@Au–perfluorohexane–PEG	Ultrasound-induced cytoclasis, contrast-intensified ultrasound (US) imaging and US-guided high intensity focused ultrasound (HIFU) surgical therapy	*Ex vivo* and *in vivo* ultrasound imaging guided HIFU on rabbit VX2 xenograft; *in vivo* thermal ablation of the tumor	[261]
Positron–emission tomography (PET)	Fe_3O_4–AuNPs–NOTA-^{64}Cu/anti-EGFR	PET/MR imaging of epidermal growth factor receptor-positive tumors	*In vitro* and *in vivo* targeting for tumor cells and contrast agent in PET/MR imaging in EGFR-expressing tumor bearing mice	[255]

Conclusions and future perspectives

The specific features related to silver and gold nano-sized particles strongly recommend such structures for potential biomedical applications. Their specific use in designing and assessing of novel bionanomaterials is clearly going to be an ongoing endeavor. We make this assumption given the immediate demand of novel and personalized therapeutic strategies and the distinctive size-dependent properties assigned to both Ag and Au nanodimensional particles. The peculiar features of these structures have lately been intensively investigated and the reported data (particularly, favorable interaction with human tissues) recommend them as potential candidates for manifold biomedical applications, including specific and accurate diagnosis platforms.

Even though the current healthcare practice embraces rather a conventional approach, the promising results provided by novel engineered nanosystems based on AgNPs and AuNPs seems to gain healthcare practitioners' interest with respect to the development of patient-oriented therapies. Regarding future perspectives of AgNPs and AuNPs in diagnosis applications and not limited to, a new trend will certainly be followed when considering the latest research studies in this domain: green-synthesized biocompatible nanoparticles, improved biological interactions, limited toxic or side effects, maximized physico-chemical specific features.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

[1] Alharbi KK, Al-Sheikh YA. Role and implications of nanodiagnostics in the changing trends of clinical diagnosis. Saudi J Biol Sci, 2014, 21(2):109–117.

[2] Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, Cohen J, Findlay D, Gyssens I, Heure OE, Kahlmeter G, Kruse H, Laxminarayan R, Liébana E, López-Cerero L, MacGowan A, Martins M, Rodríguez-Baño J, Rolain JM, Segovia C, Sigauque B, Taconelli E, Wellington E, Vila J. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect, 2015, 6:22–29.

[3] Heffernan DS, Fox ED. Advancing technologies for the diagnosis and management of infections. Surg Clin North Am, 2014, 94(6):1163–1174.

[4] Jin Z, Jiang Q, Wang L. Biomarkers for gastric cancer: progression in early diagnosis and prognosis (review). Oncol Lett, 2015, 9(4):1502–1508.

[5] Marengo E, Robotti E. Biomarkers for pancreatic cancer: recent achievements in proteomics and genomics through classical and multivariate statistical methods. World J Gastroenterol, 2014, 20(37):13325–13342.

[6] Popper HH, Ryska A, Tímár J, Oleszewski W. Molecular testing in lung cancer in the era of precision medicine. Transl Lung Cancer Res, 2014, 3(5):291–300.

[7] Esfahani M, Ataei N, Panjehpour M. Biomarkers for evaluation of prostate cancer prognosis. Asian Pac J Cancer Prev, 2015, 16(7):2601–2611.

[8] Davidson B, Tropé CG. Ovarian cancer: diagnostic, biological and prognostic aspects. Womens Health (Lond Engl), 2014, 10(5):519–533.

[9] Bashour SI, William WN, Patel S, Rao G, Strom E, McAleer MF, Guha-Thakurta N, Conrad C, Ibrahim NK. Chapter 1: Brain metastasis from solid tumors. In: Hayat MA (ed). Brain metastases from primary tumors: epidemiology, biology, and therapy. Vol. 2, Academic Press (Elsevier, Inc.), 2015, 3–29.

[10] Vatner RE, Formenti SC. Myeloid-derived cells in tumors: effects of radiation. Semin Radiat Oncol, 2015, 25(1):18–27.

[11] Sodergren SC, White A, Efficace F, Sprangers M, Fitzsimmons D, Bottomley A, Johnson CD. Systematic review of the side effects associated with tyrosine kinase inhibitors used in the treatment of gastrointestinal stromal tumours on behalf of the EORTC Quality of Life Group. Crit Rev Oncol Hematol, 2014, 91(1):35–46.

[12] Ansari D, Gustafsson A, Andersson R. Update on the management of pancreatic cancer: surgery is not enough. World J Gastroenterol, 2015, 21(11):3157–3165.

[13] Grover S, Balogun OD, Yamoah K, Groen R, Shah M, Rodin D, Olson AC, Slone JS, Shulman LN, Coleman CN, Hahn SM. Training global oncologists: addressing the global cancer control problem. Front Oncol, 2015, 5:80.

[14] Kourou K, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J, 2014, 13:8–17.

[15] Farshad-Amacker NA, Farshad M, Winklehner A, Andreisek G. MR imaging of degenerative disc disease. Eur J Radiol, 2015, 84(9):1768–1776.

[16] Aikawa E, Schoen FJ. Chapter 9: Calcific and degenerative heart valve disease. In: Willis M, Homeister J, Stone J (eds). Cellular and molecular pathobiology of cardiovascular disease. Academic Press (Elsevier, Inc.), 2014, 161–180.

[17] Gendelman HE, Anantharam V, Bronich T, Ghaisas S, Jin H, Kanthasamy AG, Liu X, McMillan J, Mosley RL, Narasimhan B, Mallapragada SK. Nanoneuromedicines for degenerative, inflammatory, and infectious nervous system diseases. Nanomedicine, 2015, 11(3):751–767.

[18] Chen CK, Yu HT, Soong YK, Lee CL. New perspectives on preimplantation genetic diagnosis and preimplantation genetic screening. Taiwan J Obstet Gynecol, 2014, 53(2):146–150.

[19] Assou S, Aït-Ahmed O, El Messaoudi S, Thierry AR, Hamamah S. Non-invasive pre-implantation genetic diagnosis of X-linked disorders. Med Hypotheses, 2014, 83(4):506–508.

[20] Evans MI, Andriole S, Evans SM. Genetics: update on prenatal screening and diagnosis. Obstet Gynecol Clin North Am, 2015, 42(2):193–208.

[21] Wright CF, Fitzgerald TW, Jones WD, Clayton S, McRae JF, van Kogelenberg M, King DA, Ambridge K, Barrett DM, Bayzetinova T, Bevan AP, Bragin E, Chatzimichali EA, Gribble S, Jones P, Krishnappa N, Mason LE, Miller R, Morley KI, Parthiban V, Prigmore E, Rajan D, Sifrim A, Swaminathan GJ, Tivey AR, Middleton A, Parker M, Carter NP, Barrett JC, Hurles ME, FitzPatrick DR, Firth HV; DDD study. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet, 2015, 385(9975):1305–1314.

[22] Binns C. Introduction to nanoscience and nanotechnology. Wiley Survival Guides in Engineering and Science, 2010.

[23] Ramsden JJ. Chapter 1: What is nanotechnology? In: Ramsden JJ (ed). Applied nanotechnology – the conversion of research results to products. 2nd edition, William Andrew, Elsevier, Inc., 2014, 3–12.

[24] Safari J, Zarnegar Z. Advanced drug delivery systems: nanotechnology of health design. A review. J Saudi Chem Soc, 2014, 18(2):85–99.

[25] Kim KS, Duncan B, Creran B, Rotello VM. Triggered nanoparticles as therapeutics. NanoToday, 2013, 8(4):439–447.

[26] Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J. Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci, 2014, 9(6):304–316.

[27] Dukes KD, Christensen KA, Chumanov G. Core-shell silver nanoparticles for optical labeling of cells. Anal Biochem, 2014, 458:43–48.

[28] Kumar N, Kumar R. Chapter 2: Nano-based drug delivery and diagnostic systems. In: Kumar N, Kumar R (eds). Nanotechnology and nanomaterials in the treatment of life-threatening diseases. William Andrew, Elsevier, Inc., 2014, 53–107.

[29] Cabral H, Miyata K, Kishimura A. Nanodevices for studying nano-pathophysiology. Adv Drug Deliv Rev, 2014, 74:35–52.

[30] Yu H, Chen Y. Chapter 10: Nanotechnology for DNA and RNA delivery. In: Webster TJ (ed). Nanomedicine – technologies and applications. Woodhead Publishing, Elsevier, Inc., 2012, 302–325.

[31] Ibraheem D, Elaissari A, Fessi H. Gene therapy and DNA delivery systems. Int J Pharm, 2014, 459(1–2):70–83.

[32] Kang L, Gao Z, Huang W, Jin M, Wang Q. Nanocarrier-mediated co-delivery of chemotherapeutic drugs and gene agents for cancer treatment. Acta Pharm Sin B, 2015, 5(3): 169–175.

[33] Bose A, Wong TW. Chapter 11: Nanotechnology-enabled drug delivery for cancer therapy. In: Thomas S, Grohens Y, Ninan N (eds). Nanotechnology applications for tissue engineering. William Andrew, Elsevier, Inc., 2015, 173–193.

[34] Sampogna G, Guraya SY, Forgione A. Regenerative medicine: historical roots and potential strategies in modern medicine. J Microsc Ultrastruct, 2015, 3(3):101–107.

[35] Shajkumar A. Chapter 17: Future of nanotechnology in tissue engineering. In: Thomas S, Grohens Y, Ninan N (eds). Nanotechnology applications for tissue engineering. William Andrew, Elsevier, Inc., 2015, 289–306.

[36] Rai M, Gade A, Yadav A. Chapter 1: Biogenic nanoparticles: an introduction to what they are, how they are synthesized and their applications. In: Rai M, Duran N (eds). Metal nanoparticles in microbiology. Springer, 2011, 1–2.

[37] Schröfel A, Kratošová G, Šafařík I, Šafaříková M, Raška I, Shor LM. Applications of biosynthesized metallic nanoparticles – a review. Acta Biomater, 2014, 10(10):4023–4042.

[38] Edmundson MC, Capeness M, Horsfall L. Exploring the potential of metallic nanoparticles within synthetic biology. N Biotechnol, 2014, 31(6):572–578.

[39] Kuppusamy P, Yusoff MM, Maniam GP, Govindan N. Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications – an updated report. Saudi Pharm J, 2014, December 8.

[40] Maldonado CR, Salassa L, Gomez-Blanco N, Mareque-Rivas JC. Nano-functionalization of metal complexes for molecular imaging and anticancer therapy. Coord Chem Rev, 2013, 257(19–20):2668–2688.

[41] Alexander JW. History of the medical use of silver. Surg Infect (Larchmt), 2009, 10(3):289–292.
[42] Nedelcu IA, Ficai A, Sonmez M, Ficai D, Oprea O, Andronescu E. Silver based materials for biomedical applications. Curr Org Chem, 2014, 18(2):173–184.
[43] Prabhu S, Poulose EK. Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. Int Nano Lett, 2012, 2:32.
[44] Tran QH, Nguyen VQ, Le AT. Silver nanoparticles: synthesis, properties, toxicology, applications and perspectives. Adv Nat Sci Nanosci Nanotechnol, 2013, 4():1–20.
[45] Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv, 2009, 27(1):76–83.
[46] Guzman M, Dille J, Godet S. Synthesis and antibacterial activity of silver nanoparticles against Gram-positive and Gram-negative bacteria. Nanomedicine, 2012, 8(1):37–45.
[47] El-Zahry MR, Mahmoud A, Refaat IH, Mohamed HA, Bohlmann H, Lendl B. Antibacterial effect of various shapes of silver nanoparticles monitored by SERS. Talanta, 2015, 138:183–189.
[48] Ahmed S, Ahmad M, Swami BL, Ikram S. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: a green expertise. J Adv Res, 2015, March 9.
[49] Lee WY, Lee DG. Chapter 16: A novel fungicidal action of silver nanoparticles: apoptosis induction. In: Ray M, Kon K (eds). Nanotechnology in diagnosis, treatment and prophylaxis of infectious diseases. Academic Press, Elsevier, Inc., 2015, 269–281.
[50] Sironmani A, Daniel K. Chapter 20: Silver nanoparticles – universal multifunctional nanoparticles for bio sensing, imaging for diagnostics and targeted drug delivery for therapeutic applications. In: Kapetanovic IM (ed). Drug discovery and development – present and future. InTech, 2011, 466–488.
[51] Wei L, Lu J, Xu H, Patel A, Chen ZS, Chen G. Silver nanoparticles: synthesis, properties, and therapeutic applications. Drug Discov Today, 2015, 20(5):595–601.
[52] Martínez-Gutierrez F, Thi EP, Silverman JM, de Oliveira CC, Svensson SL, Vanden Hoek A, Sánchez EM, Reiner NE, Gaynor EC, Pryzdial EL, Conway EM, Orrantia E, Ruiz F, Av-Gay Y, Bach H. Antibacterial activity, inflammatory response, coagulation and cytotoxicity effects of silver nanoparticles. Nanomedicine, 2012, 8(3):328–336.
[53] Hebeish A, El-Rafie MH, El-Sheikh MA, Seleem AA, El-Naggar ME. Antimicrobial wound dressing and anti-inflammatory efficacy of silver nanoparticles. Int J Biol Macromol, 2014, 65:509–515.
[54] Ravindran A, Chandran P, Khan AS. Biofunctionalized silver nanoparticles: advances and prospects. Colloids Surf B Biointerfaces, 2013, 105:342–352.
[55] Larguinho M, Baptista PV. Gold and silver nanoparticles for clinical diagnostics – from genomics to proteomics. J Proteomics, 2012, 75(10):2811–2823.
[56] El-Nour KMMA, Eftaiha A, Al-Warthan A, Ammar RAA. Synthesis and applications of silver nanoparticles. Arab J Chem, 2010, 3(3):135–140.
[57] Ghorbani HR, Safekordi AA, Attar H, Sorkhabadi SMR. Biological and non-biological methods for silver nanoparticles synthesis. Chem Biochem Eng Q, 2011, 25(3):317–326.
[58] Sergeev GB, Klabunde KJ. Chapter 2: Synthesis and stabilization of nanoparticles. In: Sergeev GB, Klabunde KJ (eds). Nanochemistry. 2nd edition, Elsevier, 2013, 11–43.
[59] Shinde M, Pawar A, Karmakar S, Seth T, Raut V, Rane S, Bhoraskar S, Amalnerkar D. Uncapped silver nanoparticles synthesized by DC arc thermal plasma technique for conductor paste formulation. J Nanopart Res, 2009, 11(8):2043–2047.
[60] Shinde M, Patil R, Karmakar S, Bhoraskar S, Rane S, Gade W, Amalnerkar D. Antimicrobial properties of uncapped silver nanoparticles synthesized by DC arc thermal plasma technique. J Nanosci Nanotechnol, 2012, 12(2):887–893.
[61] Seo JH, Hong BG. Thermal plasma synthesis of nano-sized powders. Nucl Eng Technol, 2012, 44(1):9–20.
[62] Orozco Carmona V, Martínez Pérez C, de Lima R, Fernandes Fraceto L, Romero García J, Ledezma Pérez A, Marke S, Rodríguez González C, Hurtado Macías A, Martínez-Villafañe A. Effect of silver nanoparticles in a hydroxyapatite coating applied by atmospheric plasma spray. Int J Electrochem Sci, 2014, 9(12):74741–7494.
[63] Borra JP, Jidenko N, Hou J, Weber A. Vaporization of bulk metals into single-digit nanoparticles by non-thermal plasma filaments in atmospheric pressure dielectric barrier discharges. J Aerosol Sci, 2015, 79:109–125.
[64] Hattori Y, Nomura S, Mukasa S, Toyota H, Inoue T, Usui T. Synthesis of tungsten oxide, silver, and gold nanoparticles by radio frequency plasma in water. J Alloy Compd, 2013, 578:148–152.
[65] Syromotina DS, Surmeneva MA, Gorodzha SN, Pichugin VF, Ivanova AA, Grubova IY, Kravchuk KS, Gogolinskii KV, Prymak O, Epple M, Surmenev RA. Physical-mechanical characteristics of RF magnetron sputter-deposited coatings based on silver-doped hydroxyapatite. Russ Phys J, 2014, 56(10):1198–1205.
[66] Reddy PN, Reddy MHP, Pierson JF, Uthanna S. Characterization of silver oxide films formed by reactive RF sputtering at different substrate temperatures. ISRN Optics, 2014, 2014: 684317.
[67] Raypah ME, Ahmed NM. Characterization of porous silicon thin films passivated by a nano-silver layer. Mater Sci Semicond Process, 2015, 31:235–239.
[68] Ashkarran AA. A novel method for synthesis of colloidal silver nanoparticles by arc discharge in liquid. Curr Appl Phys, 2012, 10(6):1442–1447.
[69] Tseng KH, Lee HL, Liao CY, Chen KC, Lin HS. Rapid and efficient synthesis of silver nanofluid using electrical discharge machining. J Nanomater, 2013, 2013:174939.
[70] Etman MA. Parametric study of silver nanoparticles production using submerged arc-discharge technique in de-ionized water. Nanosci Nanotechnol, 2013, 3(3):56–61.
[71] Hajivaliei M. Using electrical arc discharge method to prepare Ag-TiO_2 nanoparticles and study its photocatalytic activity. Indian J Pure Appl Phys, 2015, 53(5):311–315.
[72] Stepanov AL, Trifonov AA, Osin YN, Valeev VF, Nuzhdin VI. Fabrication of nanoporous silicon by Ag^+-ion implantation. Nanosci Nanoeng, 2013, 1(3):134–138.
[73] Yang Y, Zhang C, Song Y, Zhang L, Gou J, Meng Y, Zhang H, Ma Y. Effects of irradiation defects on the nucleation of silver nanoparticles in spinel. Vacuum, 2014, 99:115–118.
[74] Osés J, Palacio JF, Kulkarni S, Medrano A, García JA, Rodríguez R. Antibacterial PVD coatings doped with silver by ion implantation. Appl Surf Sci, 2014, 310:56–61.
[75] Koo HY, Yi JH, Kim JH, Ko YN, Hong YJ, Kang YC, Kim BK. Size-controlled silver-glass composite powders with nanometer size prepared by flame spray pyrolysis. Powder Technol, 2011, 2017(1–3):362–369.
[76] Shih SJ, Chien IC. Preparation and characterization of nanostructured silver particles by one-step spray pyrolysis. Powder Technol, 2013, 237:436–441.
[77] Janković B, Stopić S, Bogović J, Friedrich B. Kinetic and thermodynamic investigations of non-isothermal decomposition process of a commercial silver nitrate in an argon atmosphere used as the precursors for ultrasonic spray pyrolysis (USP): the mechanistic approach. Chem Eng Process Process Intensif, 2014, 82():71–87.
[78] Donnelly T, Lunney JG. Confined laser ablation for single-shot nanoparticle deposition of silver. Appl Surf Sci, 2013, 282:133–137.
[79] Rhim JW, Wang LF, Lee Y, Hong SI. Preparation and characterization of bio-nanocomposite films of agar and silver nanoparticles: laser ablation method. Carbohydr Polym, 2014, 103():456–465.
[80] Vinod M, Gopchandran KG. Au, Ag and Au:Ag colloidal nanoparticles synthesized by pulsed laser ablation as SERS substrates. Prog Nat Sci Mater Int, 2014, 24(6):569–578.
[81] Lei L, Liu X, Yin Y, Sun Y, Yu M, Shang J. Antibacterial Ag–SiO_2 composite films synthesized by pulsed laser deposition. Mater Lett, 2014, 130:79–82.
[82] Boutinguiza M, Comesaña R, Lusquiños F, Riveiro A, del Val J, Pou J. Production of silver nanoparticles by laser ablation in open air. Appl Surf Sci, 2015, 336:108–111.
[83] Sahoo PK, Kamal SSK, Kumar TJ, Sreedhar B, Singh AK, Srivastava SK. Synthesis of silver nanoparticles using facile wet chemical route. Defence Sci J, 2009, 59(4):447–455.
[84] Sergeev GB, Klabunde KJ. Chapter 2: Synthesis and stabilization of nanoparticles. In: Sergeev GB, Klabunde KJ (eds). Nanochemistry. 2nd edition, Elsevier, 2013, 13–18.

[85] Khan Z, Al-Thabaiti SA, Obaid AY, Al-Youbi AO. Preparation and characterization of silver nanoparticles by chemical reduction method. Colloids Surf B Biointerfaces, 2011, 82(2): 513–517.
[86] Van Dong P, Ha CH, Binh LT, Kasbohm J. Chemical synthesis and antibacterial activity of novel-shaped silver nanoparticles. Int Nano Lett, 2012, 2:9.
[87] Khan Z, Al-Thabaiti SA, El-Mossalamy EH, Obaid AY. Studies on the kinetics of growth of silver nanoparticles in different surfactant solutions. Colloids Surf B Biointerfaces, 2009, 73(2): 284–288.
[88] Khan Z, Hussain JI, Hashmi AA, Al-Thabaiti SA. Preparation and characterization of silver nanoparticles using aniline. Arab J Chem, 2013, May 10.
[89] Hussain JI, Kumar S, Hashmi AA, Khan Z. Silver nanoparticles: preparation, characterization, and kinetics. Adv Mater Lett, 2011, 2(3):188–194.
[90] Aswathy B, Avadhani GS, Sumithra IS, Suji S, Sony G. Microwave assisted synthesis and UV–Vis spectroscopic studies of silver nanoparticles synthesized using vanillin as a reducing agent. J Mol Liq, 2011, 159(2):165–169.
[91] Chen J, Wang J, Zhang X, Jin Y. Microwave-assisted green synthesis of silver nanoparticles by carboxymethyl cellulose sodium and silver nitrate. Mater Chem Phys, 2008, 108(2–3): 421–424.
[92] de Matos RA, da Silva Cordeiro T, Samad RE, Bonfante Sicchieri L, Vieira Júnior ND, Coronato Courrol L. Synthesis of silver nanoparticles using agar–agar water solution and femtosecond pulse laser irradiation. Colloids Surf A Physicochem Eng Asp, 2013, 423:58–62.
[93] Zhao X, Xia Y, Li Q, Ma X, Quan F, Geng C, Han Z. Microwave-assisted synthesis of silver nanoparticles using sodium alginate and their antibacterial activity. Colloids Surf A Physicochem Eng Asp, 2014, 444:180–188.
[94] Ashraf S, Abbasi AZ, Pfeiffer C, Hussain SZ, Khalid ZM, Gil PR, Parak WJ, Hussain I. Protein-mediated synthesis, pH-induced reversible agglomeration, toxicity and cellular interaction of silver nanoparticles. Colloids Surf B Biointerfaces, 2013, 102:511–518.
[95] Montazer M, Alimohammadi F, Shamei A, Rahimi MK. *In situ* synthesis of nano silver on cotton using Tollens' reagent. Carbohydr Polym, 2012, 87(2):1706–1712.
[96] Yang G, Xie J, Hong F, Cao Z, Yang X. Antimicrobial activity of silver nanoparticle impregnated bacterial cellulose membrane: effect of fermentation carbon sources of bacterial cellulose. Carbohydr Polym, 2012, 87(1):839–845.
[97] Rabinal MK, Kalasad MN, Praveenkumar K, Bharadi VR, Bhikshavartimath AM. Electrochemical synthesis and optical properties of organically capped silver nanoparticles. J Alloy Compd, 2013, 562:43–47.
[98] Biswal J, Misra N, Borde LC, Sabharwal S. Synthesis of silver nanoparticles in methacrylic acid solution by gamma radiolysis and their application for estimation of dopamine at low concentrations. Radiat Phys Chem, 2013, 83:67–73.
[99] Perni S, Hakala V, Prokopovich P. Biogenic synthesis of antimicrobial silver nanoparticles capped with L-cysteine. Colloids Surf A Physicochem Eng Asp, 2014, 460:219–224.
[100] Kashiwagi Y, Yamamoto M, Nakamoto M. Facile size-regulated synthesis of silver nanoparticles by controlled thermolysis of silver alkylcarboxylates in the presence of alkylamines with different chain lengths. J Colloid Interface Sci, 2006, 300(1):169–175.
[101] Stevanović MM, Škapin SD, Bračko I, Milenković M, Petković J, Filipič M, Uskoković DP. Poly(lactide-*co*-glycolide)/silver nanoparticles: synthesis, characterization, antimicrobial activity, cytotoxicity assessment and ROS-inducing potential. Polymer, 2012, 53(14):2818–2828.
[102] Reyes PY, Espinoza JA, Treviño ME, Saade H, López RG. Synthesis of silver nanoparticles by precipitation in bicontinuous microemulsions. J Nanomater, 2010, 2010:948941.
[103] Lah NAC, Johan MR. Facile shape control synthesis and optical properties of silver nanoparticles stabilized by Daxad 19 surfactant. Appl Surf Sci, 2011, 257(17):7494–7500.
[104] Li X, Shen J, Du A, Zhang Z, Gao G, Yang H, Wu J. Facile synthesis of silver nanoparticles with high concentration *via* a CTAB-induced silver mirror reaction. Colloids Surf A Physicochem Eng Asp, 2012, 400:73–79.
[105] Castonguay A, Kakkar AK. Dendrimer templated construction of silver nanoparticles. Adv Colloid Interface Sci, 2010, 160(1–2):76–87.
[106] Sergeev GB, Klabunde KJ. Chapter 2: Synthesis and stabilization of nanoparticles. In: Sergeev GB, Klabunde KJ (eds). Nanochemistry. 2nd edition, Elsevier, 2013, 18–22.
[107] Mănoiu VS, Aloman A. Obtaining silver nanoparticles by sonochemical methods. UPB Sci Bull B, 2010, 72(2):179–186.
[108] Wani IA, Ganguly A, Ahmed J, Ahmad T. Silver nanoparticles: ultrasonic wave assisted synthesis, optical characterization and surface area studies. Mater Lett, 2011, 65(3):520–522.
[109] Darroudi M, Zak AK, Muhamad MR, Ming HN, Hakimi M. Green synthesis of colloidal silver nanoparticles by sonochemical method. Mater Lett, 2012, 66(1):117–120.
[110] Kshirsagar P, Sangaru SS, Malvindi MA, Martiradonna L, Cingolani R, Pompa PP. Synthesis of highly stable silver nanoparticles by photoreduction and their size fractionation by phase transfer method. Colloids Surf A Physicochem Eng Asp, 2011, 392(1):264–270.
[111] Yahyaei B, Azizian S. Rapid photogeneration of silver nanoparticles in ethanolic solution: a kinetic study. Spectrochim Acta A Mol Biomol Spectrosc, 2013, 101:343–348.
[112] Hsu YC, Chen YM, Lin WL, Lan YF, Chan YN, Lin JJ. Hierarchical synthesis of silver nanoparticles and wires by copolymer templates and visible light. J Colloid Interface Sci, 2010, 352(1):81–86.
[113] Krajczewski J, Joubert V, Kudelski A. Light-induced transformation of citrate-stabilized silver nanoparticles: photochemical method of increase of SERS activity of silver colloids. Colloids Surf A Physicochem Eng Asp, 2014, 456: 41–48.
[114] Omer MAA, Saion E, Gar-elnabi MEM, Abdalla EAA, Dahlan KM, Yousif YM. Gamma radiation synthesis and characterization of polyvinyl alcohol/silver nanocomposites film. J Sci Technol, 2011, 12(1):104–110.
[115] Akhavan A, Sheikh N, Khoylou F, Naimian F, Ataeivarjovi E. Synthesis of antimicrobial silver/hydroxyapatite nanocomposite by gamma irradiation. Radiat Phys Chem, 2014, 98: 46–50.
[116] Lee JH, Park BE, Lee YM, Hwang SH, Ko WB. Synthesis of fullerene[C_{60}]-silver nanoparticles using various non-ionic surfactants under microwave irradiation. Curr Appl Phys, 2009, 9(2 Suppl):e152–e156.
[117] Forough M, Farhadi K. Biological and green synthesis of silver nanoparticles. Turk J Eng Environ Sci, 2010, 34:281–287.
[118] Mittal AK, Chisti Y, Banerjee UC. Synthesis of metallic nanoparticles using plant extracts. Biotechnol Adv, 2013, 31(2):346–356.
[119] Kharissova OV, Dias HVR, Kharisov BI, Pérez BO, Jiménez Pérez VM. The greener synthesis of nanoparticles. Trends Biotechnol, 2013, 31(4):240–248.
[120] Shukla VK, Singh RP, Pandey AC. Black pepper assisted biomimetic synthesis of silver nanoparticles. J Alloy Compd, 2010, 507(1):L13–L16.
[121] Mallikarjuna K, Sushma NJ, Narasimha G, Manoj L, Raju BDP. Phytochemical fabrication and characterization of silver nanoparticles by using Pepper leaf broth. Arab J Chem, 2014, 7(6):1099–1103.
[122] Rastogi L, Arunachalam J. Sunlight based irradiation strategy for rapid green synthesis of highly stable silver nanoparticles using aqueous garlic (*Allium sativum*) extract and their antibacterial potential. Mater Chem Phys, 2011, 129(1–2):558–563.
[123] Abbasi M, Saeed F, Rafique U. Preparation of silver nanoparticles from synthetic and natural sources: remediation model for PAHs. IOP Conf Ser Mater Sci Eng, 2014, 60: 012061.
[124] Mondal S, Varma S, Bamola VD, Naik SN, Mirdha BR, Padhi MM, Mehta N, Mahapatra SC. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (*Ocimum sanctum* Linn.) leaf extract on healthy volunteers. J Ethnopharmacol, 2011, 136(3):452–456.
[125] Subba Rao Y, Kotakadi VS, Prasad TNVKV, Reddy AV, Sai Gopal DVR. Green synthesis and spectral characterization of silver nanoparticles from Lakshmi tulasi (*Ocimum sanctum*) leaf extract. Spectrochim Acta A Mol Biomol Spectrosc, 2013, 103:156–159.

[126] Roy N, Gaur A, Jain A, Bhattacharya S, Rani V. Green synthesis of silver nanoparticles: an approach to overcome toxicity. Environ Toxicol Pharmacol, 2013, 36(3):807–812.
[127] Raut RW, Mendhulkar VD, Kashid SB. Photosensitized synthesis of silver nanoparticles using *Withania somnifera* leaf powder and silver nitrate. J Photochem Photobiol B, 2014, 132:45–55.
[128] Nadagouda MN, Iyanna N, Lalley J, Han C, Dionysiou DD, Varma RS. Synthesis of silver and gold nanoparticles using antioxidants from blackberry, blueberry, pomegranate, and turmeric extracts. ACS Sustain Chem Eng, 2014, 2(7):1717–1723.
[129] Roopan SM, Rohit, Madhumitha G, Rahuman AA, Kamaraj C, Bharathi A, Surendra TV. Low-cost and eco-friendly phytosynthesis of silver nanoparticles using *Cocos nucifera* coir extract and its larvicidal activity. Ind Crop Prod, 2013, 43: 631–635.
[130] Mariselvam R, Ranjitsingh AJ, Usha Raja Nanthini A, Kalirajan K, Padmalatha C, Mosae Selvakumar P. Green synthesis of silver nanoparticles from the extract of the inflorescence of *Cocos nucifera* (Family: *Arecaceae*) for enhanced antibacterial activity. Spectrochim Acta A Mol Biomol Spectrosc, 2014, 129:537–541.
[131] Bankar A, Joshi B, Kumar AR, Zinjarde S. Banana peel extract mediated novel route for the synthesis of silver nanoparticles. Colloids Surf A Physicochem Eng Asp, 2010, 368(1–3):58–63.
[132] Ibrahim HMM. Green synthesis and characterization of silver nanoparticles using banana peel extract and their antimicrobial activity against representative microorganisms. J Radiat Res Appl Sci, 2015, 8(3):265–275.
[133] El-Shanshoury AERR, ElSilk SE, Ebeid ME. Extracellular biosynthesis of silver nanoparticles using *Escherichia coli* ATCC 8739, *Bacillus subtilis* ATCC 6633, and *Streptococcus thermophilus* ESh1 and their antimicrobial activities. ISRN Nanotechnol, 2011, 2011:385480.
[134] Gurunathan S, Kalishwaralal K, Vaidyanathan R, Venkataraman D, Pandian SRK, Muniyandi J, Hariharan N, Eom SH. Biosynthesis, purification and characterization of silver nanoparticles using *Escherichia coli*. Colloids Surf B Biointerfaces, 2009, 74(1):328–335.
[135] Mokhtari N, Daneshpajouh S, Seyedbagheri S, Atashdehghan R, Abdi K, Sarkar S, Minaian S, Shahverdi HR, Shahverdi AR. Biological synthesis of very small silver nanoparticles by culture supernatant of *Klebsiella pneumonia*: the effects of visible-light irradiation and the liquid mixing process. Mater Res Bull, 2009, 44(6):1415–1421.
[136] Kalpana D, Lee YS. Synthesis and characterization of bactericidal silver nanoparticles using cultural filtrate of simulated microgravity grown *Klebsiella pneumoniae*. Enzyme Microb Technol, 2013, 52(3):151–156.
[137] Kumar CG, Mamidyala SK. Extracellular synthesis of silver nanoparticles using culture supernatant of *Pseudomonas aeruginosa*. Colloids Surf B Biointerfaces, 2011, 84(2):462–466.
[138] Nanda A, Saravanan M. Biosynthesis of silver nanoparticles from *Staphylococcus aureus* and its antimicrobial activity against MRSA and MRSE. Nanomedicine, 2009, 5(4):452–456.
[139] Vigneshwaran N, Ashtaputre NM, Varadarajan PV, Nachane RP, Paralikar KM, Balasubramanya RH. Biological synthesis of silver nanoparticles using the fungus *Aspergillus flavus*. Mater Lett, 2007, 61(6):1413–1418.
[140] Saravanan M, Nanda A. Extracellular synthesis of silver bionanoparticles from *Aspergillus clavatus* and its antimicrobial activity against MRSA and MRSE. Colloids Surf B Biointerfaces, 2010, 77(2):214–218.
[141] Mishra A, Tripathy SK, Yun SI. Bio-synthesis of gold and silver nanoparticles from *Candida guilliermondii* and their antimicrobial effect against pathogenic bacteria. J Nanosci Nanotechnol, 2011, 11(1):243–248.
[142] Ahmad T, Wani IA, Manzoor N, Ahmed J, Asiri AM. Biosynthesis, structural characterization and antimicrobial activity of gold and silver nanoparticles. Colloids Surf B Biointerfaces, 2013, 107:227–234.
[143] Korbekandi H, Ashari Z, Iravani S, Abbasi S. Optimization of biological synthesis of silver nanoparticles using *Fusarium oxysporum*. Iran J Pharm Res, 2013, 12(3):289–298.
[144] Singh D, Rathod V, Ninganagouda S, Hiremath J, Kulkarni P. Biosynthesis of silver nanoparticle by endophytic fungi *Penicillium* sp. isolated from *Curcuma longa* (turmeric) and its antibacterial activity against pathogenic Gram negative bacteria. J Pharm Res, 2013, 7:448–453.
[145] Singh P, Raja RB. Biological synthesis and characterization of silver nanoparticles using the fungus *Trichoderma harzianum*. Asian J Exp Biol Sci, 2011, 2(4):600–605.
[146] Devi TP, Kulanthaivel S, Kamil D, Borah JL, Prabhakaran N, Srinivasa N. Biosynthesis of silver nanoparticles form *Trichoderma* species. Indian J Exp Biol, 2013, 51(7):543–547.
[147] Ren F, Campbell J, Rorrer GL, Wang AX. Surface-enhanced Raman spectroscopy sensors from nanobiosilica with self-assembled plasmonic nanoparticles. IEEE J Sel Top Quantum Electron, 2014, 20(3):6900806.
[148] Liu JW, Wang JL, Huang WR, Yu L, Ren XF, Wen WC, Yu SH. Ordering Ag nanowire arrays by a glass capillary: a portable, reusable and durable SERS substrate. Sci Rep, 2012, 2:987.
[149] Zheng J, Jiao A, Yang R, Li H, Li J, Shi M, Ma C, Jiang Y, Deng L, Tan W. Fabricating reversible and regenerable Raman-active substrate with a biomolecule-controlled DNA nanomachine. J Am Chem Soc, 2012, 134(49):19957–19960.
[150] Kandjani AE, Mohammadtaheri M, Thakkar A, Bhargava SK, Bansal V. Zinc oxide/silver nanoarrays as reusable SERS substrates with controllable 'hot-spots' for highly reproducible molecular sensing. J Colloid Interface Sci, 2014, 436:251–257.
[151] Krajczewski J, Kołątaj K, Kudelski A. Light-induced growth of various silver seed nanoparticles: a simple method of synthesis of different silver colloidal SERS substrates. Chem Phys Lett, 2015, 625:84–90.
[152] Yazdi SH, White IM. A nanoporous optofluidic microsystem for highly sensitive and repeatable surface enhanced Raman spectroscopy detection. Biomicrofluidics, 2012, 6(1):14105–14159.
[153] Messina GC, Malerba M, Zilio P, Miele E, Dipalo M, Ferrara L, De Angelis F. Hollow plasmonic antennas for broadband SERS spectroscopy. Beilstein J Nanotechnol, 2015, 6:492–498.
[154] De Bonis A, Galasso A, Ibris N, Sansone M, Santagata A, Teghil R. Ultra-short pulsed laser deposition of thin silver films for surface enhanced Raman scattering. Surf Coat Technol, 2012, 207:279–285.
[155] Wu HJ, Henzie J, Lin WC, Rhodes C, Li Z, Sartorel E, Thorner J, Yang P, Groves JT. Membrane-protein binding measured with solution-phase plasmonic nanocube sensors. Nat Methods, 2012, 9(12):1189–1191.
[156] Xiao N, Wang C, Yu C. A self-referencing detection of microorganisms using surface enhanced Raman scattering nanoprobes in a test-in-a-tube platform. Biosensors, 2013, 3(3):312–326.
[157] Karabchevsky A, Tsapovsky L, Marks RS, Abdulhalim I. Study of immobilization procedure on silver nanolayers and detection of estrone with diverged beam surface plasmon resonance (SPR) imaging. Biosensors (Basel), 2013, 3(1): 157–170.
[158] Zhou W, Ma Y, Yang H, Ding Y, Luo X. A label-free biosensor based on silver nanoparticles array for clinical detection of serum p53 in head and neck squamous cell carcinoma. Int J Nanomedicine, 2011, 6:381–386.
[159] Robson AF, Hupp TR, Lickiss F, Ball KL, Faulds K, Graham D. Nanosensing protein allostery using a bivalent mouse double minute two (MDM2) assay. Proc Natl Acad Sci U S A, 2012, 109(21):8073–8078.
[160] Zhang Y, Gao G, Liu H, Fu H, Fan J, Wang K, Chen Y, Li B, Zhang C, Zhi X, He L, Cui D. Identification of volatile biomarkers of gastric cancer cells and ultrasensitive electrochemical detection based on sensing interface of Au–Ag alloy coated MWCNTs. Theranostics, 2014, 4(2):154–162.
[161] Hong ML, Li LJ, Han HX, Chu X. A label-free fluorescence assay for trypsin based on the electron transfer between oligonucleotide-stabilized Ag nanoclusters and cytochrome c. Anal Sci, 2014, 30(8):811–815.
[162] Ma K, Yuen JM, Shah NC, Walsh JT Jr, Glucksberg MR, Van Duyne RP. *In vivo*, transcutaneous glucose sensing using surface-enhanced spatially offset Raman spectroscopy:

multiple rats, improved hypoglycemic accuracy, low incident power, and continuous monitoring for greater than 17 days. Anal Chem, 2011, 83(23):9146–9152.
[163] Joshi AC, Markad GB, Haram SK. Rudimentary simple method for the decoration of graphene oxide with silver nanoparticles: their application for the amperometric detection of glucose in the human blood samples. Electrochim Acta, 2015, 161:108–114.
[164] Zhang S, Han L, Hou C, Li C, Lang Q, Han L, Liu A. Novel glucose sensor with Au@Ag heterogeneous nanorods based on electrocatalytic reduction of hydrogen peroxide at negative potential. J Electroanal Chem, 2015, 742:84–89.
[165] Ma H, Song K, Zhou L, Zhao X. A naked eye refractive index sensor with a visible multiple peak metamaterial absorber. Sensors (Basel), 2015, 15(4):7454–7461.
[166] Yao Y, Jie K, Zhou Y, Xue M. Water-soluble pillar[6]arene stabilized silver nanoparticles: preparation and application in amino acid detection. Tetrahedron Lett, 2014, 55(20):3195–3199.
[167] Contino A, Maccarrone G, Zimbone M, Musumeci P, Calcagno L, Pannitteri S. Fine tuning the pH triggers the enantiorecognition of underivatized amino acids by silver nanoparticles: a novel approach based on the focused use of solution equilibria. J Colloid Interface Sci, 2015, 443:30–35.
[168] Liu JJ, Song XR, Wang YW, Zheng AX, Chen GN, Yang HH. Label-free and fluorescence turn-on aptasensor for protein detection *via* target-induced silver nanoclusters formation. Anal Chim Acta, 2012, 749:70–74.
[169] Fojan P, Hanif M, Bartling S, Hartmann H, Barke I, Popok VN. Supported silver clusters as nanoplasmonic transducers for protein sensing. Sensor Actuat B Chem, 2015, 212:377–381.
[170] Abel B, Aslan K. Immobilization of enzymes to silver island films for enhanced enzymatic activity. J Colloid Interface Sci, 2014, 415:133–142.
[171] Szymanski MS, Porter RA. Preparation and quality control of silver nanoparticle–antibody conjugate for use in electrochemical immunoassays. J Immunol Methods, 2013, 387(1–2): 262–269.
[172] Song W, Li H, Liu H, Wu Z, Qiang W, Xu D. Fabrication of streptavidin functionalized silver nanoparticle decorated graphene and its application in disposable electrochemical sensor for immunoglobulin E. Electrochem Commun, 2013, 31:16–19.
[173] El Khoury EE, Abiad M, Kassaify ZG, Patra D. Green synthesis of curcumin conjugated nanosilver for the applications in nucleic acid sensing and anti-bacterial activity. Colloids Surf B Biointerfaces, 2015, 127:274–280.
[174] Zhao H, Wang L, Zhu J, Wei H, Jiang W. Label-free nucleic acids detection based on DNA templated silver nanoclusters fluorescent probe. Talanta, 2015, 138:163–168.
[175] Gwinn E, Schultz D, Copp SM, Swasey S. DNA-protected silver clusters for nanophotonics. Nanomaterials, 2015, 5(1): 180–207.
[176] Braun GB, Friman T, Pang HB, Pallaoro A, Hurtado de Mendoza T, Willmore AM, Kotamraju VR, Mann AP, She ZG, Sugahara KN, Reich NO, Teesalu T, Ruoslahti E. Etchable plasmonic nanoparticle probes to image and quantify cellular internalization. Nat Mater, 2014, 13(9):904–911.
[177] Gao S, Chen D, Li Q, Ye J, Jiang H, Amatore C, Wang X. Near-infrared fluorescence imaging of cancer cells and tumors through specific biosynthesis of silver nanoclusters. Sci Rep, 2014, 4:4384.
[178] Mukherjee S, Chowdhury D, Kotcherlakota R, Patra S, B V, Bhadra MP, Sreedhar B, Patra CR. Potential theranostics application of bio-synthesized silver nanoparticles (4-in-1 system). Theranostics, 2014, 4(3):316–335.
[179] Xia X, Li W, Zhang Y, Xia Y. Silica-coated dimers of silver nanospheres as surface-enhanced Raman scattering tags for imaging cancer cells. Interface Focus, 2013, 3: 20120092.
[180] Zou J, Hannula M, Misra S, Feng H, Labrador RH, Aula AS, Hyttinen J, Pyykkö I. Micro CT visualization of silver nanoparticles in the middle and inner ear of rat and transportation pathway after transtympanic injection. J Nanobiotechnology, 2015, 13:5.
[181] Chen LQ, Xiao SJ, Peng L, Wu T, Ling J, Li YF, Huang CZ. Aptamer-based silver nanoparticles used for intracellular protein imaging and single nanoparticle spectral analysis. J Phys Chem B, 2010, 114(10):3655–3659.
[182] Hu H, Li H, Zhao Y, Dong S, Li W, Qiang W, Xu D. Aptamer-functionalized silver nanoparticles for scanometric detection of platelet-derived growth factor-BB. Anal Chim Acta, 2014, 812:152–160.
[183] Tawa K, Yasui C, Hosokawa C, Aota H, Hishii J. *In situ* sensitive fluorescence imaging of neurons cultured on a plasmonic dish using fluorescence microscopy. ACS Appl Mater Interfaces, 2014, 6(22):20010–20015.
[184] Chen Z, Shin D, Chen S, Mikhail K, Hadass O, Tomlison BN, Korkin D, Shyu CR, Cui J, Anthony DC, Gu Z. Histological quantitation of brain injury using whole slide imaging: a pilot validation study in mice. PLoS One, 2014, 9(3):e92133.
[185] Shi J, Sun X, Lin Y, Zou XY, Li Z, Liao Y, Du M, Zhang H. Endothelial cell injury and dysfunction induced by silver nanoparticles through oxidative stress *via* IKK/NF-κB pathways. Biomaterials, 2014, 35(24):6657–6666.
[186] Okochi M, Kuboyama M, Tanaka M, Honda H. Design of a dual-function peptide probe as a binder of angiotensin II and an inducer of silver nanoparticle aggregation for use in label-free colorimetric assays. Talanta, 2015, 142:235–239.
[187] Tao W, Gill HS. M2e-immobilized gold nanoparticles as influenza A vaccine: role of soluble M2e and longevity of protection. Vaccine, 2015, 33(20):2307–2315.
[188] Fytianos K, Rodriguez-Lorenzo L, Clift MJ, Blank F, Vanhecke D, von Garnier C, Petri-Fink A, Rothen-Rutishauser B. Uptake efficiency of surface modified gold nanoparticles does not correlate with functional changes and cytokine secretion in human dendritic cells *in vitro*. Nanomedicine, 2015, 11(3):633–644.
[189] Wang F, Zhang W, Shen Y, Huang Q, Zhou D, Guo S. Efficient RNA delivery by integrin-targeted glutathione responsive polyethyleneimine capped gold nanorods. Acta Biomater, 2015, 23:136–146.
[190] Zhao X, Huang Q, Jin Y. Gold nanorod delivery of LSD1 siRNA induces human mesenchymal stem cell differentiation. Mater Sci Eng C Mater Biol Appl, 2015, 54:142–149.
[191] Banu H, Sethi DK, Edgar A, Sheriff A, Rayees N, Renuka N, Faheem SM, Premkumar K, Vasanthakumar G. Doxorubicin loaded polymeric gold nanoparticles targeted to human folate receptor upon laser photothermal therapy potentiates chemotherapy in breast cancer cell lines. J Photochem Photobiol B, 2015, 149:116–128.
[192] Zhang X, Teodoro JG, Nadeau JL. Intratumoral gold-doxorubicin is effective in treating melanoma in mice. Nanomedicine, 2015, 11(6):1365–1375.
[193] Tarapacki C, Karshafian R. Enhancing laser therapy using PEGylated gold nanoparticles combined with ultrasound and microbubbles. Ultrasonics, 2015, 57:36–43.
[194] Elbialy NS, Fathy MM, Khalil WM. Doxorubicin loaded magnetic gold nanoparticles for *in vivo* targeted drug delivery. Int J Pharm, 2015, 490(1–2):190–199.
[195] Arunkumar P, Raju B, Vasantharaja R, Vijayaraghavan S, Preetham Kumar B, Jeganathan K, Premkumar K. Near infra-red laser mediated photothermal and antitumor efficacy of doxorubicin conjugated gold nanorods with reduced cardiotoxicity in Swiss albino mice. Nanomedicine, 2015, 11(6):1435–1444.
[196] Ge S, Zhang Y, Zhang L, Liang L, Liu H, Yan M, Huang J, Yu J. Ultrasensitive electrochemical cancer cells sensor based on trimetallic dendritic Au@PtPd nanoparticles for signal amplification on lab-on-paper device. Sensor Actuat B Chem, 2015, 220:665–672.
[197] German N, Kausaite-Minkstimiene A, Ramanavicius A, Semashko T, Mikhailova R, Ramanaviciene A. The use of different glucose oxidases for the development of an amperometric reagentless glucose biosensor based on gold nanoparticles covered by polypyrrole. Electrochim Acta, 2015, 169:326–333.
[198] Kowalczyk A, Wagner B, Karbarz M, Nowicka AM. A dual DNA biosensor based on two redox couples with a hydrogel sensing platform functionalized with carboxyl groups and gold nanoparticles. Sensor Actuat B Chem, 2015, 208:220–227.
[199] Zhang J, Li C, Zhang X, Huo S, Jin S, An FF, Wang X, Xue X, Okeke CI, Duan G, Guo F, Zhang X, Hao J, Wang PC, Zhang J, Liang XJ. *In vivo* tumor-targeted dual-modal fluo-

rescence/CT imaging using a nanoprobe co-loaded with an aggregation-induced emission dye and gold nanoparticles. Biomaterials, 2015, 42:103–111.
[200] Park J, Park J, Ju EJ, Park SS, Choi J, Lee JH, Lee KJ, Shin SH, Ko EJ, Park I, Kim C, Hwang JJ, Lee JS, Song SY, Jeong SY, Choi EK. Multifunctional hollow gold nanoparticles designed for triple combination therapy and CT imaging. J Control Release, 2015, 207:77–85.
[201] Zhao HY, Liu S, He J, Pan CC, Li H, Zhou ZY, Ding Y, Huo D, Hu Y. Synthesis and application of strawberry-like Fe_3O_4-Au nanoparticles as CT-MR dual-modality contrast agents in accurate detection of the progressive liver disease. Biomaterials, 2015, 51:194–207.
[202] Lam ATN, Ganbold EO, Cho KH, Kang D, Joo SW. Raman spectroscopy of gold nanoparticle conjugates of cosmetic ingredient kinetin. Vibrat Spectrosc, 2014, 73:15–18.
[203] Li Y, Schluesener HJ, Xu S. Gold nanoparticle-based biosensors. Gold Bull, 2010, 43(1):29–41.
[204] Hanžić N, Jurkin T, Maksimović A, Gotić M. The synthesis of gold nanoparticles by a citrate-radiolytical method. Radiat Phys Chem, 2015, 106:77–82.
[205] E X, Zhang Y, Zou JJ, Zhang X, Wang L, Shape evolution in Brust–Schiffrin synthesis of Au nanoparticles. Mater Lett, 2014, 118:196–199.
[206] Luty-Błocho M, Fitzner K, Hessel V, Löb P, Maskos M, Metzke D, Pacławski K, Wojnicki M. Synthesis of gold nanoparticles in an interdigital micromixer using ascorbic acid and sodium borohydride as reducers. Chem Eng J, 2011, 171(1):279–290.
[207] Malkar VV, Mukherjee T, Kapoor S. Synthesis of silver nanoparticles in aqueous aminopolycarboxylic acid solutions *via* γ-irradiation and hydrogen reduction. Mater Sci Eng C Mater Biol Appl, 2014, 44:87–91.
[208] Babu PJ, Sharma P, Saranya S, Bora U. Synthesis of gold nanoparticles using ethanolic leaf extract of *Bacopa monnieri* and UV irradiation. Mater Lett, 2013, 93:431–434.
[209] Seol SK, Kim D, Jung S, Chang WS, Bae YM, Lee KH, Hwu Y. Effect of citrate on poly(vinyl pyrrolidone)-stabilized gold nanoparticles formed by PVP reduction in microwave (MW) synthesis. Mater Chem Phys, 2012, 137(1):135–139.
[210] Nguyen DT, Kim DJ, So MG, Kim KS. Experimental measurements of gold nanoparticle nucleation and growth by citrate reduction of $HAuCl_4$. Adv Powder Technol, 2010, 21(2):111–118.
[211] Wu H, Ji X, Zhao L, Yang S, Xie R, Yang W. Shape evolution of citrate capped gold nanoparticles in seeding approach. Colloids Surf A Physicochem Eng Asp, 2012, 415:174–179.
[212] Doyen M, Bartik K, Bruylants G. UV-Vis and NMR study of the formation of gold nanoparticles by citrate reduction: observation of gold-citrate aggregates. J Colloid Interface Sci, 2013, 399:1–5.
[213] Costa Lima SA, Reis S. Temperature-responsive polymeric nanospheres containing methotrexate and gold nanoparticles: a multi-drug system for theranostic in rheumatoid arthritis. Colloids Surf B Biointerfaces, 2015, 133:378–387.
[214] Pajović JD, Dojčilović R, Božanić DK, Kaščáková S, Réfrégiers M, Dimitrijević-Branković S, Vodnik VV, Milosavljević AR, Piscopiello E, Luyt AS, Djoković V. Tryptophan-functionalized gold nanoparticles for deep UV imaging of microbial cells. Colloids Surf B Biointerfaces, 2015, 135:742–750.
[215] Hu Y, Song Y, Wang Y, Di J. Electrochemical synthesis of gold nanoparticles onto indium tin oxide glass and application in biosensors. Thin Solid Films, 2011, 519(19):6605–6609.
[216] German N, Ramanavicius A, Ramanaviciene A. Electrochemical deposition of gold nanoparticles on graphite rod for glucose biosensing. Sensor Actuat B Chem, 2014, 203: 25–34.
[217] Nie K, Hu J, Pang W, Zhu Q. Poly(amidoamine)-G5 dendrimers/noble metal gold hybrid nanoparticles prepared by γ-ray irradiation. Mater Lett, 2007, 61(17):3567–3570.
[218] Anh NT, Phu DV, Duy NN, Du BD, Hien NQ. Synthesis of alginate stabilized gold nanoparticles by γ-irradiation with controllable size using different Au^{3+} concentration and seed particles enlargement. Radiat Phys Chem, 2010, 79(4):405–408.
[219] Chili MM, Rajasekhar Pullabhotla VSR, Revaprasadu N. Synthesis of PVP capped gold nanoparticles by the UV-irradiation technique. Mater Lett, 2011, 65(17–18):2844–2847.
[220] Bhuvanasree SR, Harini D, Rajaram A, Rajaram R. Rapid synthesis of gold nanoparticles with *Cissus quadrangularis* extract using microwave irradiation. Spectrochim Acta A Mol Biomol Spectrosc, 2013, 106:190–196.
[221] Soliwoda K, Rosowski M, Tomaszewska E, Tkacz-Szczesna B, Celichowski G, Psarski M, Grobelny J. Synthesis of monodisperse gold nanoparticles *via* electrospray-assisted chemical reduction method in cyclohexane. Colloids Surf A Physicochem Eng Asp, 2015, 482:148–153.
[222] Maciulevičius M, Vinčiūnas A, Brikas M, Butsen A, Tarasenka N, Tarasenko N, Račiukaitis G. On-line characterization of gold nanoparticles generated by laser ablation in liquids. Phys Procedia, 2013, 41:531–538.
[223] Barry M, Ding B, Jung Y, Reddy BVK, Phuoc TX, Chyu MK. Pulsed nanosecond laser ablation of gold in deionized water and aqueous chitosan solution. Opt Lasers Eng, 2014, 55: 59–68.
[224] Jin Y, Li Z, Hu L, Shi X, Guan W, Du Y. Synthesis of chitosan-stabilizez gold nanoparticles by atmospheric plasma. Carbohydr Polym, 2013, 91(1):152–156.
[225] Shang Y, Min C, Hu J, Wang T, Liu H, Hu Y. Synthesis of gold nanoparticles by reduction of $HAuCl_4$ under UV irradiation. Solid State Sci, 2013, 15:17–23.
[226] Sen IK, Maity K, Islam SS. Green synthesis of gold nanoparticles using a glucan of an edible mushroom and study of catalytic activity. Carbohydr Polym, 2013, 91(2):518–528.
[227] Kuppusamy P, Yusoff MM, Ichwan SJA, Parine NR, Maniam GP, Govindan N. *Commelina nudiflora* L. edible weed as a novel source for gold nanoparticles synthesis and studies on different physical–chemical and biological properties. J Ind Eng Chem, 2015, 27:59–67.
[228] Gholami-Shabani M, Shams-Ghahfarokhi M, Gholami-Shabani Z, Akbarzadeh A, Riazi G, Ajdari S, Amani A, Razzaghi-Abyaneh M. Enzymatic synthesis of gold nanoparticles using sulfite reductase purified from *Escherichia coli*: a green eco-friendly approach. Process Biochem, 2015, 50(7):1076–1085.
[229] Senapati S, Syed A, Moeez S, Kumar A, Ahmad A. Intracellular synthesis of gold nanoparticles using alga *Tetraselmis kochinensis*, Mater Lett, 2012, 79:116–118.
[230] Bathrinarayanan PV, Thangavelu D, Muthukumarasamy VK, Munusamy C, Gurunathan B. Biological synthesis and characterization of intracellular gold nanoparticles using biomass of *Aspergillus fumigatus*. J Bull Mater Sci, 2013, 36(7):1201–1205.
[231] Ji J, Zhou Z, Zhao X, Sun J, Sun X. Electrochemical sensor based on molecularly imprinted film at Au nanoparticles-carbon nanotubes modified electrode for determination of cholesterol. Biosens Bioelectron, 2015, 66:590–595.
[232] Yola ML, Eren T, Atar N. Molecularly imprinted electrochemical biosensor based on Fe@Au nanoparticles involved in 2-aminoethanethiol functionalized multi-walled carbon nanotubes for sensitive determination of cefexime in human plasma. Biosens Bioelectron, 2014, 60:277–285.
[233] Peng HP, Hu Y, Liu P, Deng YN, Wang P, Chen W, Liu AL, Chen YZ, Lin XH. Label-free electrochemical DNA biosensor for rapid detection of mutidrug resistance gene based on Au nanoparticles/toluidine blue–graphene oxide nanocomposites. Sensor Actuat B Chem, 2015, 207(Pt A):269–276.
[234] Bagheryan Z, Raoof JB, Ojani R. Development of a new gquadruplex biosensor with the functionalized SBA-15-Au nanoparticles: a platform for selecting gquadruplex-binding ligands. Sensor Actuat B Chem, 2015, 213:124–130.
[235] Sun Y, He X, Ji J, Jia M, Wang Z, Sun X. A highly selective and sensitive electrochemical CS–MWCNTs/Au-NPs composite DNA biosensor for *Staphylococcus aureus* gene sequence detection. Talanta, 2015, 141:300–306.
[236] Huang H, Bai W, Dong C, Guo R, Liu Z. An ultrasensitive electrochemical DNA biosensor based on graphene/Au nanorod/polythionine for human papillomavirus DNA detection. Biosens Bioelectron, 2015, 68:442–446.
[237] Shao Y, Xu S, Zheng X, Wang Y, Xu W. Optical fiber LSPR biosensor prepared by gold nanoparticle assembly on polyelectrolyte multilayer. Sensors (Basel), 2010, 10(4):3585–3596.

[238] Saigusa M, Tsuboi K, Konosu Y, Ashizawa M, Tanioka A, Matsumoto H. Highly sensitive local surface plasmon resonance in anisotropic Au nanoparticles deposited on nanofibers. J Nanomater, 2015, 2015:829273.
[239] Chuang YC, Li JC, Chen S, Liu TY, Kuo CH, Huang WT, Lin CS. An optical biosensing platform for proteinase activity using gold nanoparticles. Biomaterials, 2010, 31(23):6087–6095.
[240] Ding J, Lu Z, Wang R, Shen G, Xiao L. Piezoelectric immunosensor with gold nanoparticles enhanced competitive immunoreaction technique for 2,4-dichlorophenoxyacetic acid quantification. Sensor Actuat B Chem, 2014, 193:568–573.
[241] Chen SH, Wu VCH, Chuang YC, Lin CS. Using oligonucleotide-functionalized Au nanoparticles to rapidly detect foodborne pathogens on a piezoelectric biosensor. J Microbiol Methods, 2008, 73(1):7–17.
[242] ***. Nanospectra: Tumor ablation using Aurolase® Therapy. Nanospectra Biosciences, Inc., http://www.nanospectra.com/index.html.
[243] Zhong J, Wen L, Yang S, Xiang L, Chen Q, Xing D. Imaging-guided high-efficient photoacoustic tumor therapy with targeting gold nanorods. Nanomedicine, 2015, 11(6):1499–1509.
[244] Yasmin Z, Khachatryan E, Lee YH, Maswadi S, Glickman R, Nash KL. *In vitro* monitoring of oxidative processes with self-aggregating gold nanoparticles using all-optical photoacoustic spectroscopy. Biosens Bioelectron, 2015, 64:676–682.
[245] Mallidi S, Kim S, Karpiouk A, Joshi PP, Sokolov K, Emelianov S. Visualization of molecular composition and functionality of cancer cells using nanoparticle-augmented ultrasound-guided photoacoustics. Photoacoustics, 2015, 3(1):26–34.
[246] Gao Y, Li Y, Chen J, Zhu S, Liu X, Zhou L, Shi P, Niu D, Gu J, Shi J. Multifunctional gold nanostar-based nanocomposite: synthesis and application for noninvasive MR-SERS imaging-guided photothermal ablation. Biomaterials, 2015, 60:31–41.
[247] Zhao L, Kim TH, Kim HW, Ahn JC, Kim SY. Surface-enhanced Raman scattering (SERS)-active gold nanochains for multiplex detection and photodynamic therapy of cancer. Acta Biomater, 2015, 20:155–164.
[248] Rand D, Ortiz V, Liu Y, Derdak Z, Wands JR, Tatíček M, Rose-Petruck C. Nanomaterials for X-ray imaging: gold nanoparticle enhancement of X-ray scatter imaging of hepatocellular carcinoma. Nano Lett, 2011, 11(7):2678–2683.
[249] Chien CC, Chen HH, Lai SF, Wu KC, Cai X, Hwu Y, Petibois C, Chu Y, Margaritondo G. Gold nanoparticles as high-resolution X-ray imaging contrast agents for the analysis of tumor-related micro-vasculature. J Nanobiotechnology, 2012, 10:10.
[250] Silvestri A, Polito L, Bellani G, Zambelli V, Jumde RP, Psaro R, Evangelisti C. Gold nanoparticles obtained by aqueous digestive ripening: their application as X-ray contrast agents. J Colloid Interface Sci, 2015, 439:28–33.
[251] Ahn S, Jung SY, Lee SJ. Gold nanoparticle contrast agents in advanced X-ray imaging technologies. Molecules, 2013, 18(5):5858–5890.
[252] Hola K, Markova Z, Zoppellaro G, Tucek J, Zboril R. Tailored functionalization of iron oxide nanoparticles for MRI, drug delivery, magnetic separation and immobilization of biosubstances. Biotechnol Adv, 2015, Feb 14.
[253] Yang M, Cheng K, Qi S, Liu H, Jiang Y, Jiang H, Li J, Chen K, Zhang H, Cheng Z. Affibody modified and radiolabeled gold-iron oxide hetero-nanostructures for tumor PET, optical and MR imaging. Biomaterials, 2013, 34(11):2796–2806.
[254] Wang H, Zheng L, Peng C, Guo R, Shen M, Shi X, Zhang G. Computed tomography imaging of cancer cells using acetylated dendrimer-entrapped gold nanoparticles. Biomaterials, 2011, 32(11):2979–2988.
[255] Peng C, Zheng L, Chen Q, Shen M, Guo R, Wang H, Cao X, Zhang G, Shi X. PEGylated dendrimer-entrapped gold nanoparticles for *in vivo* blood pool and tumor imaging by computed tomography. Biomaterials, 2012, 33(4):1107–1119.
[256] Chen Q, Li K, Wen S, Liu H, Peng C, Cai H, Shen M, Zhang G, Shi X. Targeted CT/MR dual mode imaging of tumors using multifunctional dendrimer-entrapped gold nanoparticles. Biomaterials, 2013, 34(21):5200–5209.
[257] Jing L, Liang X, Deng Z, Feng S, Li X, Huang M, Li C, Dai Z. Prussian blue coated gold nanoparticles for simultaneous photoacoustic/CT bimodal imaging and photothermal ablation of cancer. Biomaterials, 2014, 35(22):5814–5821.
[258] Zhang S, Gong M, Zhang D, Yang H, Gao F, Zou L. Thiol-PEG-carboxyl-stabilized Fe_2O_3/Au nanoparticles targeted to CD105: synthesis, characterization and application in MR imaging of tumor angiogenesis. Eur J Radiol, 2014, 83(7):1190–1198.
[259] Wen S, Li K, Cai H, Chen Q, Shen M, Huang Y, Peng C, Hou W, Zhu M, Zhang G, Shi X. Multifunctional dendrimer-entrapped gold nanoparticles for dual mode CT/MR imaging applications. Biomaterials, 2013, 34(5):1570–1580.
[260] Li J, Hu Y, Yang J, Wei P, Sun W, Shen M, Zhang G, Shi X. Hyaluronic acid-modified Fe_3O_4@Au core/shell nanostars for multimodal imaging and photothermal therapy of tumors. Biomaterials, 2015, 38:10–21.
[261] Wang X, Chen H, Zheng Y, Ma M, Chen Y, Zhang K, Zeng D, Shi J. Au-nanoparticle coated mesoporous silica nanocapsule-based multifunctional platform for ultrasound mediated imaging, cytoclasis and tumor ablation. Biomaterials, 2013, 34(8):2057–2068.

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