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A repertoire of biomedical applications of noble metal nanoparticles

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Noble metals comprise any of several metallic chemical elements that are outstandingly resistant to corrosion and oxidation, even at elevated temperatures. This group is not strictly defined, but the tentative list includes ruthenium, rhodium, palladium, silver, osmium, iridium, platinum and gold, in order of atomic number. The emergence of noble metal nanotechnology is attracting huge interest from the scientific community and has led to an unprecendented expansion of research and exploration of applications in electrochemistry, catalysis and biomedicine. Noble metal nanocomposites can be synthesised both by top-down and bottom up approaches, as well as via organism-assisted routes, and subsequently modified appropriately for the field of use. Nanoscale analogues of gold, silver, platinum, and palladium in particular, have gained primary importance owing to their excellent intrinsic properties and diversity of applications; they offer unique functional attributes, which are quite unlike the bulk material. Modulation of noble metal nanoparticles in terms of size, shape and surface functionalisation has endowed them with unusual capabilities and manupulation at the chemical level, which can lead to changes in their electrical, chemical, optical, spectral and other intrinsic properties. In this comprehensive review, we highlight recent advances in the adaptation of noble metal nanomaterials and their applications in therapeutics, diagnostics, sensing, and environmental monitoring.

Introduction

In chemistry, noble metals are defined as metals that are outstanding resistant to corrosion and oxidation even at elevated temperatures and these include the metals of groups VIIb, VIII and 1b of the second and third transition series of the periodic table i.e. rhodium (Rh), ruthenium (Ru), palladium (Pd), silver (Ag), osmium (Os), iridium (Ir), platinum (Pt), and gold (Au).[1] Noble metals have a long and rich history, which probably dates back to as early as the Egyptian First Dynasty. They belong to a class of elements that has found a wide range of applications encompassing aerospace, electronic industries and most importantly, the health sector[2–5]. The amalgamation of nanoscience and biotechnology has spawned a growing field of research in the form of nanobiotechnology. In this new arena, the technological leap of synthesising and controlling materials at nanoscale level has provided an immense opportunity to progress medical and healthcare treatment, diagnostics and therapies.[6] Noble metals are eclectic non-toxic agents in the sense that they have a wide diversity of biomedical applications, which include use in highly sensitive diagnostic assays,[7] thermal ablation as radiotherapy enhancers,[8–11] and drug and gene delivery vehicles.[12–18] Among all noble metals, Au and Ag nanoparticles are most extensively studied due to the well-established synthesis routes, their relatively higher content in the earth crust, and better safety profile. Nanoparticle-based systems are now becoming an effective tool in "Theranostics" (i.e. simultaneous diagnosis and therapy) because of their unique properties of excellent penetration and traceability within the body, which allows for a more efficient therapy with a reduced risk of any toxic side effects in comparison to conventional therapies.[19,16,20,21] The unique characteristics of noble metal nanostructures, in terms of high surface-to-volume ratio, broad optical properties, ease of synthesis, and tunability of surface functionalisation and modification, provide an important added dimensions in bio-diagnostics, biophysical studies, biosensing and medical therapy.[16,20,21] Noble metal nanoparticles (NMN) have played an equally important role in the development of novel biosensors, to add to or enhance the accuracy and specificity of already existing biomolecular diagnostics. The physicochemical attributes of noble metals at the nanoscale level have led to the development of a wide variety of biosensors such as: (i) nanobiosensors for point care disease detection, (ii) nanoprobes for *in vivo* cell imaging, tracking and pathogenesis of disease progression and (iii) other nanobiotechnology-based tools that enhance basic biological research.[22–25]

The colloidal state of noble metals has been the subject of intensive investigations because of their effectiveness, and various questions have been raised regarding their safety profile in human body. Colloidal gold, silver, platinum, palladium, iridium, ruthenium and rhodium are easily and widely available on the market for use in combating many diseases, free radicals and bacteria. In this review, we provide an extensive literature survey covering recent developments in this field.

Synthetic Routes for NMN

The preparation of nanoparticles fundamentally follows two distinctly different approaches, top-down and bottom-up (**Scheme 1**).[26] The top-down processes involve bulk materials which are reduced to particles with nano-dimension using various physical and chemical methodologies. On the other hand, in a bottom-up approach, nanoparticles are constructed through the assembly of the atoms, the molecules, or the clusters and thus this is generically termed self-assembly.

Externally controlled tools are utilised in a top-down approach for cutting, milling and shaping the materials into the desired order and shape. Several physical methods, such as pyrolysis,[27] lithography,[28–30] thermolysis,[31,32] and radiation-induced methods[33] belong in this category. A major limitation of the top-down approach is the

imperfect surface structure of metallic nanoparticles, which substantially affects their physical and chemical properties.[34] Moreover, enormous energy is required to maintain the high pressure and high-temperature conditions during these synthetic procedures and this makes these processes expensive.

In a bottom-up methodology, the originally formed nanoparticles are subsequently assembled into the final material, using chemical as well as biological procedures. The bottom-up approach is advantageous as it provides a far better control over the final product formation with less surface deformation and more homogeneous chemical composition. Moreover, the processes are in general less expensive as well. The bottom-up approach is commonly used for wet-chemical synthesis procedures, such as chemical,[35–37] electrochemical,[38,39] polyol reduction[40] and sonochemical.[41,42] However, one major challenge associated to these processes is the purification of the nanoparticles from toxic chemicals, organic solvents and reagents for further biomedical applications.

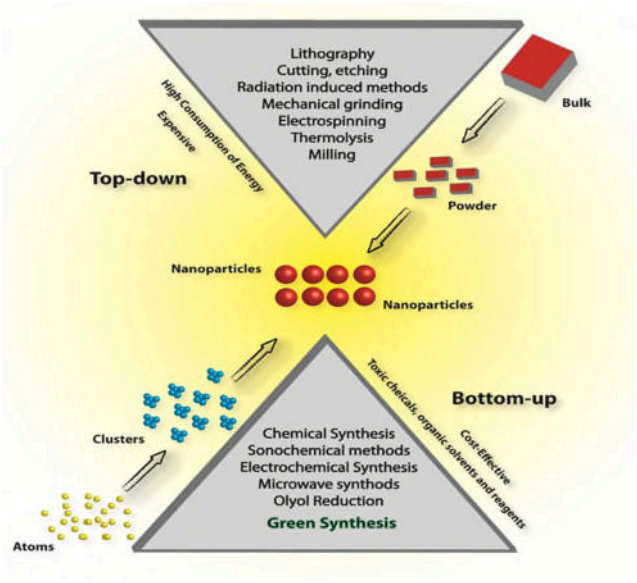
Top-down approaches

One of the commonly used protocols is micropatterning.[43] Apart from the most common approach of photolithography, various other techniques have evolved in the recent past.[44] Scanning, soft, nano-imprint, colloidal, nanosphere and E-beam lithography are among some of these new methods. In principle, all these techniques use either light, electrons, a focused beam of electrons or electrostatic forces to selectively remove nano-structures from a precursor to develop ordered arrays of nano-materials.

In a milling process, macro-scale materials are ground in a ball mill to generate particles of nano dimensions.[45] The kinetic energy transfer from balls to powder is behind the reduction in grain size. Various parameters like, type of mill, milling atmosphere, milling media, intensity, time, temperature, etc. play a crucial role in controlling the shape and size of the nanoparticles.[46] Different devices designed for various purposes have been developed in order to overcome these constrains including shaker mills, tumbler mills, vibratory mills, attrition mills, planetary mills, etc. For bulk production of nano-materials, the attrition process is highly advantageous. However, one major limitation of this process is the imperfect surface and significant crystallographic damage of the processed materials. Pyrolysis is another important technique commonly used.[47] A precursor in its vapour state is forced through an orifice with high pressure and burning. Through further processing of the obtained solid ash, nanoparticles are recovered. Pyrolysis is frequently used for the preparation of noble metal nanoparticles.[27,48] One important drawback of the method is the requirement for large amounts of energy.

Bottom-Up approaches

The most commonly utilised and easiest bottom-up approach is the chemical reduction of metal ions in solutions. In principle, an ionic salt is reduced using various reducing agents under appropriate reaction conditions and in presence of a stabilising agent.[35–37] A plethora of reducing agents, such as Na-citrate, hydrazine, hydrogen, $LiAlH_4$, $NaBH_4$, and alcohols can be used. According to Lee-Meisel method,[49] nitrate and sulphate salts are reduced using $NaBH_4$, sodium citrate, and hydrogen. The pH of the medium plays a crucial role in modulating the size and shape of the particles.[50] At high pH, owing to faster reduction, both rod and spherical nanoparticles were found, while at relatively lower pH (5-6), triangular and other polyhedral structures were obtained because of the slower reaction. Similarly, Au nanoparticles can be prepared from an aqueous solution of $HAuCl_4$ using citrate as the reducing agent.[51,52] The average particle size can be controlled by varying the ratio of reducing/stabilising agents as well as the pH of the system.[53,54] On the other hand, platinum, another important class of noble metal nanoparticles is relatively under explored. Sodium polyacrylate stabilised cubic and tetrahedral platinum nanoparticle synthesis in solution phase has been reported by El-Sayed et al.[55] A general strategy based on a chemical reduction method involving different metal combinations (cobalt, iron, and nickel) with platinum has been reported by Zhang.[56] Another popular nanoparticle fabrication process involves microemulsions. The first microemulsion-based synthesis was reported for palladium, rhodium, and platinum nanoparticles synthesis.[57] Since then, the process gained popularity owing to its ease of operation and control over the size and shape of the products.[58–60] Herein, two separate microemulsions containing salts and reducing agents are mixed together in presence of amphiphile. Inter microemulsion collision leads to the mixing of the reactants and consequently nanoparticles are formed. This strategy helps in growing nanoparticles with uniform shape and size as the microemulsions are used as a template while the nanoparticles are growing during the process. This method offers benefits to prepare thermodynamically stable and monodispersed nanoparticles.[61]



Scheme 1 Schematic presentation of the top-down and bottom-up approaches for nanoparticle synthesis.

In a laser ablation process, a solid surface is irradiated with a laser beam and the materials become heated at low laser flux and are finally evaporated or sublimated.[62] At a higher flux, the materials are converted to form plasma. The lack of any requirement to remove excess reagents as well as the possibility of metal nanoparticle synthesis in both aqueous and organic solvents has allowed the laser ablation method to emerge as a potential alternative for chemical reduction methods. There have been several reports where this process was used to prepare a variety of noble metal nanoparticles including silver, gold, and platinum.[63–65] Fast processing times,

control over the size and shape of the particles and high yields are among the major advantages of this process.

Microwave-based synthesis and electrochemical methods are the other two important approaches to be mentioned. Microwave irradiation is used for the "one-pot" preparation of metal nanoparticles from their salts and polymeric surfactant solutions.[66] It is a relatively fast and easy method with high selectivity and control over size and morphology of the end products.[67] The electrochemical method was first introduced by Reetz.[68] A metal sheet was dissolved from the anode and the metal salt thus produced was reduced on the cathode of an electrochemical cell producing the desired metal nanoparticles.[69,70] Importantly, control over the particle size can easily be achieved without any template. Considering the excess use of chemicals and solvents in the chemical synthesis of nanoparticles, greener approaches with minimal use of such hazardous chemicals have been developed. One major driving force for these greener approaches is nature's efficiency in making these nano-materials. Mimicking nature, may not be not easy, but it has allowed chemists to develop several green synthetic protocols for nanoparticle synthesis using water as the medium and proteins or carbohydrates as capping agents.[71,72] Starch has been used as both a reducing as well as a stabilising agent for the synthesis of stable silver nanoparticles.[73,74] Similarly, gold nanoparticles have been prepared utilising different biomolecules as capping agents and lactic acid as the reducing agent.[74] Chitosan, a natural biopolymer, has also been used as a reducing and stabilising agent.[75] In another "greener" approach, hydrogels of synthesised peptides and other small molecules were successfully used to create nanoparticles where the hydrogel nano-structures act as the template and help in creating the shape and size of the nanoparticles.[76,77] Das et al. prepared a tryptophan-appended peptide amphiphile able to form hydrogel where gold nanoparticles with defined shape and size could be prepared using the indole residue as the reducing agent, without the need for any external agent.[78,79]

Organism-based synthesis of NMN

The quest for the development of economically as well as environmentally benign methods led to exploration of the potential of micro-organisms in this respect.[80] Biological systems are excellent examples of hierarchical organisations of atoms or molecules and this attracted researchers to use micro-organisms as potential cell factories for nano-material preparation. Both prokaryotic (bacteria) and eukaryotic (algae, fungi, plants) species are used for this purpose.

Bacteria are often exposed to metal rich environments and have the ability to develop resistance to these extreme conditions. Thus, prokaryotes like bacteria are an automatic choice for the production of nanomaterials. *Pseudomonas stutzeri* AG259, a metal accumulating bacterium, was utilised by Klaus et al. to create intracellular nanocrystals of metallic silver and monoclinic silver sulphide.[81] Extracellular synthesis of nanoparticles was first reported by Shahverdi and co-workers.[82] Nanocrystals of silver were prepared by incubating the biomass of *Bacillus licheniformis* in presence of silver nitrate, where NADH acted as the reducing agent in presence of nitrate reductase.[83] Gold nanoparticles are also prepared by accumulation and reduction of gold salts by bacteria. *Bacillus licheniformis, Shewanella algae, Stenotrophomonas maltophilia, Lactobacillus* strains, present in the whey of butter milk are some of the examples of bacteria which have been used to produce gold nanomaterials.[84–87] In addition to these, bacteria like *Schewanella* and *Acinetobactor calcoaceticus* PUCM 1011 were utilised for the preparation of platinum nanoparticles.[88,89] Though promising in terms of its green nature and control over the shape and size of the particles, bacterial-mediated synthesis suffers from disadvantages such as difficulty in handling and low yield. In recent years, eukaryotic organisms have emerged as a better alternative for the synthesis of noble metal nanoparticles, owing to easier protocols as well as cost-effectiveness. Fungi were first tested by Sastry et al. for the preparation of metal and metal oxide nanoparticles.[90] Gold nanoparticles were prepared using *Verticillium sp.* when $AuCl_4$ was reduced within the fungal cells. *Fusarium oxysporum* was used to prepare gold and silver nanoparticles with uniform dimensions.[91] An environmentally friendly and cost-effective method for the synthesis of silver nanoparticles using cell-free filtrate of *Aspergillus flavus* was reported by Panwar and coworkers.[80] Another important biological media are the algae. Algae, like *Chlorella vulgaris* and *Pithophora oedogonia*, have been used successfully to construct silver nanoparticles.[92,93] Gold nanoparticles have been prepared involving various seaweeds like *Sargassum wightii* by Singaravelu et al.[94] Plant extracts are also attractive media for the synthesis of nanoparticles and the process has been referred to as Phytosynthesis. Live alfalfa plant can take gold ions from solid media and the secretome from live alfalfa plant can reduce gold ions to Au^0, which can be taken up by the plant and consequently used to produce gold nanoparticles.[95] Neem (*Azadirachta indica*) leaf extract was successfully used by Shankar et al. to prepare silver, gold, and bimetallic Au/Ag core–shell nanoparticles.[96] Similar plant extracts (bark, leaf, fruit, and gum) have been used by several researchers to produce a variety of noble metal nanoparticles.[97–100]

As discussed, several physical, chemical as well as biological methods have been developed for the synthesis of nanoparticles. All these processes are widely used based on the utility and applicability of the nano-products. However, the existing protocols all suffer from certain drawbacks. Thus, the development of alternative processes to fabricate nanoparticles with controlled and tuneable properties is still an open challenge.

Surface Modification and Functionalisation of NMN

NMN have attracted significant attention in various applications ranging from electronics to sensing, biolabeling, photonics, nanomedicine and catalysis, due to their electrical, chemical, optical, spectral and other intrinsic properties.[101,102,103] To increase the biocompatibility, sensing, and specific targeting of NPs, it is necessary to stabilise NPs against agglomeration and to functionalise them.[104–106] Attaching appropriate organic groups to the metal surfaces is the most common way to achieve this (**Fig. 1**). Through metal−thiolate (M−S) linkages,[107] organosulphur groups coordinate to various metals such as Ag, Cu, Fe, Au.[108] Metal−carbon (M-C=) covalent bonds using aryl diazonium as the precursors[109] have been used to stabilise metal NPs. Metal−carbene (M=C) or metal−nitrene (M=N) π bonds formed with diazo derivatives, have been utilised to functionalise various metal NPs such as Au, Pt, Ti, Ru, and Pd.[110,111] Metal−acetylide/−vinylidene bonds are formed via acetylene derivatives onto metal surfaces.[112] Surface modification or functionalisation of metal NPs can be accomplished with amines or

ammonium ions, negatively charged carboxylate groups, and phosphines.[113]

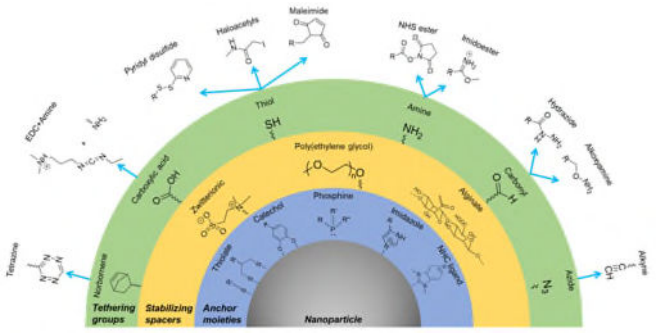


Fig. 1 Schematic illustration of representative anchor moieties, stabilizing spacers, tethering groups, and conjugation groups for functionalising noble nanoparticles. NHC = N-heterocyclic carbenes, NHS = N-Hydroxysuccinimide, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Analytical techniques for NMN characterisation

The unique properties of noble metal NPs such as thermal, electrical, chemical, and optical rely on the size, morphology and surface charge. Various techniques have been developed to characterise the metal NPs.[114] Size distribution, average particle diameter, surface charge, and shape govern the physical stability of metal NPs.[115] Scanning electron microscopy (SEM),[116] dark-field and field-emission scanning electron microscopy (FE-SEM),[117,118] transmission electron microscopy (TEM),[119] high-resolution TEM (HRTEM),[120–122] and atomic force microscopy (AFM)[123,124] are commonly utilised to estimate the size, shape, and surface morphology. Dynamic light scattering (DLS) observations enable the determination of particle sizes and their size distributions *in situ*.[125,126] Small-angle X-ray scattering (SAXS), extended X-ray absorption fine structure (EXAFS), X-ray absorption near-edge structure analysis (XANES), and electron spin resonance (ESR) provide information about the local structure and electronic properties of metal NPs with different surface chemistry and morphology.[127,128] X-ray photoelectron spectroscopy (XPS),[129] Fourier transform infrared (FTIR) spectroscopy and solid-state nuclear magnetic resonance spectroscopy (SSNMR) can be used to obtain information about surface chemistry of metal NPs.[130] Matrix-assisted laser-desorption ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS), inductively coupled plasma mass spectrometry (ICP-MS), UV–vis spectroscopy and exclusion chromatography with UV–vis detection (SEC-UV–vis) have also all been utilised to characterise various properties of nanomaterials (**Fig. 2**).[114,131,132] Energy-Dispersive X-ray spectroscopy (EDX) analysis can be used to confirm the chemical composition of the metal NPs.[119]

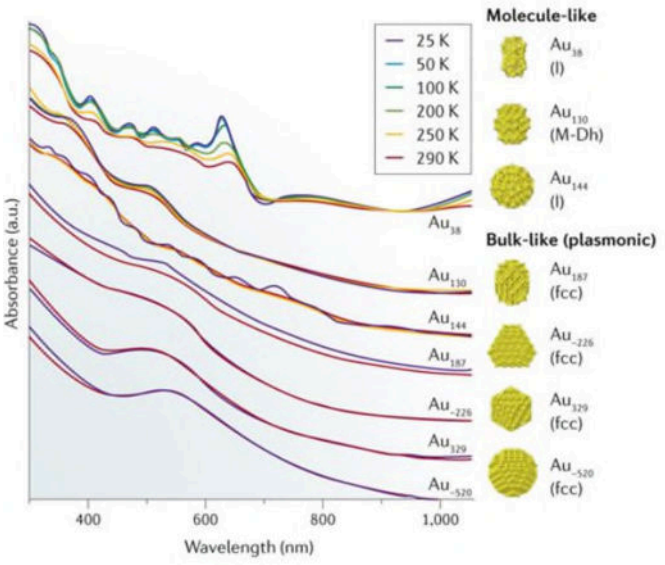


Fig. 2 Evolution of optical absorption spectra of gold clusters with various sizes, measured at different temperatures, as indicated. Au_n clusters with n = 38, 130 and 144 show discrete energy states in the spectra and have icosahedral (I) or Marks decahedral (M-Dh) structures, whereas the clusters with n = 187, ~226, 329 and ~520 have plasmonic resonances originating from their metallic band structure and a face-centered cubic (fcc) structure. Reprinted with permission from Reference[133]

Biomedical applications of NMN

Complexes of noble metals have been used as therapeutic agents since ancient times. With the advent of nanobiotechnology, there has been a surge towards the development of different kinds of nanostructures with a diverse range of biomedical applications (Fig. 3). In this regard, NMN have gained primary importance; there are several reasons for this including: (i) ease of size and shape modulation; (ii) unique optical and photothermal properties; and (iii) surface functionalisation. Since these nanomaterials can interact with biomolecules both at the surface and inside the cell, they represent an excellent repertoire of biocompatible nanoscale drugs. These NMN can be synthesised both chemically and biogenically with high efficiency,[134,135] and these engineered nanoscale versions of noble metals have inspired researchers to develop innumerable therapeutic agents for the treatment of a wide range of diseases,[136,137] where nanotechnology-based approaches have been shown that play a significant role in treatment and early diagnosis of these diseases. NMN are the most common nanobiotechnological materials used for developing biosensors for clinical diagnostics, due to their ease in fabrication, physiochemical malleability, and high surface areas,[138] allied with their unique spectral and optical properties. NMN have had a promising impact on the development of new biosensors and on enhancing the specificity and sensitivity of already existing biosensing techniques for biomolecular diagnostics (**Table 4**). Noble metal nanostructures can be engineered to specifically recognise biomolecules and provide a rapid and accurate estimation of the concentration of an analyte. This can be achieved by exploiting changes in the optical properties of noble metal colloids as a result of affinity interactions modulating their size and electronic configuration (**Fig. 8**).[139] The unique optical properties of different surface modified noble metal nano formulations have been used for targeting biological components such as DNA, RNA, cells, proteins, small organic molecules, and other biological components. This section will point out some of the unique therapeutic and diagnostic abilities of NMN.

Therapeutic efficacy of NMN

The uptake of inorganic or NMN has been studied extensively in recent years. The mechanism of cellular internalisation of noble metal nanoparticles such as gold, silver and platinum are not necessarily similar and are, at the same time, ambiguous. Size, shape, surface charge, and surface chemistry play extremely important roles in cellular uptake both *in vitro* and *in vivo.* Spherical gold nanoparticles (GNPs) exhibit greater cellular uptake than their corresponding rod structures.[140] It has been reported that 40-50 nm particles have the most effective cellular internalisation.[141,142] In a separate study, it was shown that 50 nm GNPs can enter into cells at a relatively faster rate and at a higher concentration than other sizes.[140] This observation was further validated by both *in vitro* and *in vivo* studies.[143] AsPC-1, PANC-1, and MiaPaca-2 (pancreatic cell lines) upon incubation with GNPs of varying hydrodynamic radii, exhibited the greatest uptake for 20 nm particles, as shown by TEM analysis. Another important factor which modulates cellular internalisation of noble metal nanoparticles is surface charge.[144,145] The exterior of the cell is mostly anionic; hence positively charged noble metal nanoparticles can easily traverse through the cell membrane via electrostatic interaction.[144] However, negatively charged noble metal nanoparticles have also been observed in the cell interior as a result of them passively targeting lipophilic domains.[146] One report suggests that zwitterionic noble metal nanoparticles can be a potent and highly efficient drug delivery system.[147,148]

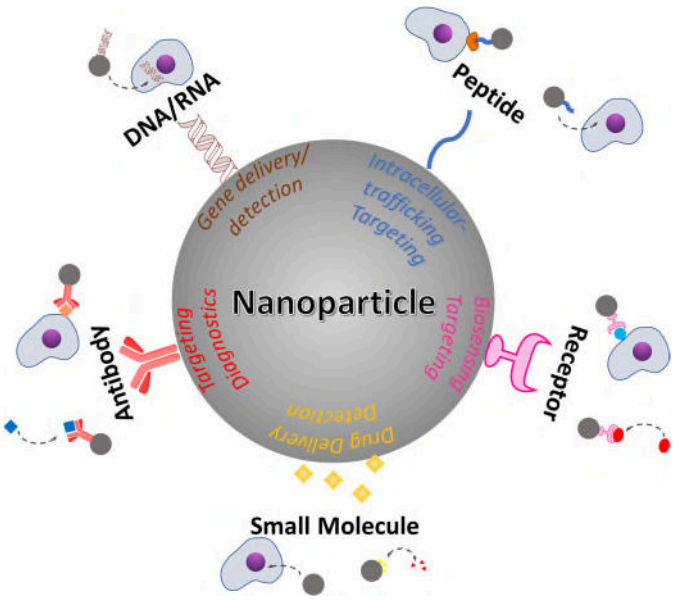


Fig. 3 Biomedical applications of nanoparticles through conjugation with various active moieties including nucleic acids, peptides, receptors, antibodies, and small molecules.

Angiogenesis has been shown to be critically involved in a number of diseases such as cancer, rheumatoid arthritis, and macular degeneration.[149,150] Under normal conditions, angiogenesis is tightly regulated by various anti-angiogenic factors such as thrombospondins (TSP-1), platelet factor 4, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor beta (TGF-β).[151] Under pathological condition, this balance is disrupted that leads to angiogenesis.[151] In such cases, there is generation of highly abnormal blood vessels, which become hyperpermeable to plasma proteins.

A number of anti-angiogenic agents have been clinically tested but they seem to target only the VEGF[152] mediated signalling.[153] Also, these agents possess serious toxicities which result in hypertension, thrombosis, and fatal hemorrhage.[149,150] Here, noble metal nanoparticles can be used as an effective anti-angiogenic agent, since they have the ability to target multiple pathways involved in angiogenesis.[154] Uncapped GNPs exhibit anti-angiogenic properties by inhibiting the activity of heparin-binding proteins such as VEGF[152] and basic fibroblast growth factor (bFGF) *in vitro* and VEGF induced angiogenesis *in vivo.*[155] It was observed that heparin-binding proteins are absorbed on the surface of the GNPs and lose their functional attributes.[156] The size of GNPs also dictates their anti-angiogenic activity; in one study it was shown that VEGF[152] preincubated with GNPs of varying size (5-20 nm) had a dramatic effect on VEGF signalling events.[157] The suppression of heparin-binding growth factors by nanoparticles has further explained their effectiveness against multiple myeloma via inhibiting VEGF- and bFGF- dependent proliferation as tested in cell lines OPM-1, RPMI-8266, and U-266. This study revealed that cells are arrested in the G1 phase of the cell cycle with an up-regulation of p21 and p27.[158] The anti-angiogenic properties of GNPs could also modulate the status of B-chronic lymphocytic leukemia (B-CLL) cells.[155] Exposure of GNPs to B-CLL cells resulted in an increase in apoptosis in a dose-dependent manner.[159] Angiogenesis also plays a crucial role in the promotion and maintenance of inflammatory diseases such as rheumatoid arthritis (RA). It has been observed that 13 nm GNPs exhibit anti-rheumatoid activity in collagen-induced arthritis in rats.[160] GNPs bind to VEGF in the synovial fluid of patients suffering from RA and affect their cellular proliferation and migration. Further, histological studies showed that there is reduction in tumour necrosis factor alpha (TNF-α) and interleukin beta (IL-β) after intra-articular administration of GNPs. Silver nanoparticles (AgNPs) have also been shown to act as an anti-angiogenic agent. AgNPs with size of 40 nm were used to study their anti-angiogenic properties in bovine retinal epithelial cells (BREC). AgNPs successfully inhibited cell proliferation and migration in VEGF induced angiogenesis in BRECs and prevented the formation of new blood vessels.[159] Furthermore, tumour bearing mice demonstrated a reduction of ascite production and suppression of tumour progression upon treatment with AgNPs.[161,162]

Cancer is one of the largest life-threatening diseases worldwide and has led to millions of deaths, most of them in developing countries. A combination of surgery, chemotherapy and radiation therapy constitutes the major treatment procedures for almost all cancer therapy. Since these conventional therapeutic regimens are whole body approach, there is significant systemic damage to healthy tissues and subsequently health-related issues.[154] In order to minimise the damage to non-cancerous tissue, noble metal nanoparticles have been utilised as a potential cancer therapeutic agent for non-invasive tumour treatment.[163] In this regard, application of a magnetic field selectively heats the nanomaterials, which allows for selective and effective destruction of tumour cells.[163] Currently, photodynamic therapy (PDT), regional hyperthermia, and radiotherapy are actively being exploited for localised cancer treatment.[101,164,165] PDT treatment is mainly achieved by focusing the light source on the affected area of the body. The spectrum of light used here is in the range of 630-900 nm, that is the near infrared region (NIR), which is readily absorbed by the tissue.[164] This range of wavelength minimises the light extinction by intrinsic chromophores in the normal or healthy tissue.[166] In regional hyperthermic tumour therapy, the cancerous cells are damaged upon exposure to elevated temperatures.[167] There is loss of membrane integrity, DNA damage, and induction of apoptosis as well as necrosis within a few hours.[168] In radiation therapy, cancer patients are treated with ionising radiations, which is effective but at the same time it is invasive with numerous side effects on healthy

tissues. Noble metal nanoparticles hold great promise as PDT, hyperthermia, and radiotherapy agents. Surface plasmon resonance (SPR) of noble metal nanoparticles has been effectively exploited for PDT anticancer treatment.[169] In one study, it has been shown that GNPs can act as PDT agents and selectively destroy cancerous cells at very low laser frequency.[170] Citrate capped GNPs (15 nm) have also been deployed as photothermal therapy (PTT) agents against A431 cells. This study showed that upon exposure to low levels of laser light, GNPs induce the destruction of the malignant cells through reactive oxygen species (ROS) mediated apoptosis (**Fig. 4a**).[171] Further, the shape of the GNPs plays an extremely important role in PDT therapy, GNPs with different geometry were tested against HUVEC cells and it was noted that gold nanorods were 100 times more potent than the other shapes tested.[172] Similarly, mice injected with GNPs had a significant reduction of deep tissue tumours after a brief exposure to NIR.[173] GNPs have been used for treatment of skin cancer; GNPs were administered into the tail vein of mice and local laser induced hyperthermia was employed for reduction and complete inhibition of skin tumours.[174] Radio frequency ablation (RFA) in conjunction with GNPs has proved to be an effective treatment strategy for liver cancer cell (HepG2) lines; here citrate coated GNPs demonstrated a time-dependent cytotoxic effect upon exposure to the RF field.[175] Noble metal nanoparticles offer an attractive advantage in radiotherapy owing to their excellent optical properties, surface plasmon resonance, and surface modalities. For example, upon X-ray irradiation, GNPs have been shown to induce cellular apoptosis by the generation of ROS.[176] This therapeutic treatment strategy has effectively increased the percentage of cancer cells killed without harming the nearby surrounding healthy tissue.[177,178] Mice injected with GNPs upon X-ray exposure exhibit a fourfold reduction in tumour size and also an extended lifetime of the animal.[179]

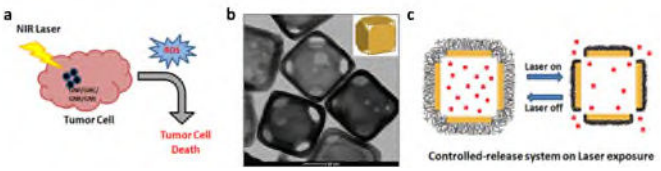


Fig. 4 (a) Schematic representation of ROS generated tumour cell death using NIR induced metal nanoparticles (b) TEM images of Au nanocages for which the surface was covered by a pNIPAAm-co-pAAm copolymer with an LSCT at 39°C. The inset shows a magnified TEM image of the corner of such a nanocage. (c) Schematic illustration of the controlled-release system (cross-sectional view): upon exposure to a near-infrared laser, the light is absorbed by the nanocage and converted into heat, leading to the collapse of smart polymeric brushes and release off loaded drugs.

Transport of drugs or therapeutic agents into the cells by GNPs have been the subject of intensive studies in biomedical treatment. Surface functionalised gold colloids have been extensively studied for interaction with the cell membrane for efficient and improved drug delivery.[145,180,181] In one report, it was observed that surface ligand rearrangement on GNPs can regulate cell membrane permeability.[146] Gold nanoparticles functionalised with an ordered arrangement of amphiphilic molecules were able to penetrate the cell membrane more efficiently than particles with a disordered arrangement of the same molecules that were entrapped in vesicular bodies. The therapeutic activity of GNPs on cells can be regulated through passive and active targeting mechanisms. Passive targeting is based on the concept of an enhanced permeability and retention (EPR) effect; here gold colloids can extravasate into the tumour stroma because of the defective vasculature and increased lymphatic drainage leading to its accumulation at the target site (**Fig. 5**).[154,182] Active targeting relies on surface tuneability of GNPs specifically designed for the target molecules to provide high specificity and selectivity.[183–185] These attributes of gold nanostructures have been developed for applications in photothermal therapy,[186–188] genetic regulation,[189–191] and drug treatment.[192,193] GNPs are considered a potential and powerful therapeutic probe for specific and selective killing of cancer cells.[194] GNPs scaffolds have been synthesised for use as transfection agents in gene therapy for curing cancer and genetic disorders. GNPs coated with oligonucleotides are being applied as intracellular gene alteration agents for controlling protein expression in cells.[195] Ribonucleic acid (RNA) modulated colloidal gold nanoparticles have been successfully tested for knockdown of luciferase activity,[196] because the conjugated nanomaterials possess an extended half-life as compared to double-stranded(ds)-RNA, demonstrating a high gene knockdown capability in cell models. Positively charged amino acid (first generation lysine dendrons) coated GNPs have proved to be effective and non-toxic transfection vectors for DNA delivery, providing up to 28 times greater effectiveness than the conventional negatively charged polylysine version.[197]

EPR debate

It is worth mentioning, however, the debate within the nanotechnology community on EPR effect. The general belief is that PEGylated nanoparticles have elongated blood circulation time and could result in enhanced EPR effect. This concept seems problematic when considering the astonishingly small number of translational products as compared to the large number of research articles produced based on this assumption.[9] It is yet to be determined that whether the intercellular or intracellular extravasation is the predominant mechanism for macromolecules accumulation within tumors, as intercellular gaps are very rare.[10] Therefore, further investigation on the extravasation mechanism of nanoparticles to tumours is required to provide useful insight and guidelines for designing nanoparticle formulations.

Targeted delivery of drugs has been carried out efficiently using gold colloids by loading drugs onto GNPs through non-covalent or covalent interactions. Drug entrapment with GNPs is achieved through the use of hydrophobic or hydrophilic pockets[198] presented by the monolayer. Polymer encapsulated GNPs provide an amphiphilic surrounding for the entrapment of hydrophobic silicon phthalocyanine 4 (Pc 4), a photodynamic therapy (PDT) agent.[199] This conjugation releases the drug efficiently and quickly and deep into tumour tissues within hours of incubation. Covalently conjugated GNPs drugs are released through glutathione (GSH) displacement[200] or through linker cleavage.[201] A GSH-mediated release strategy using 6-mercaptopurine-9-b-D-ribofuranoside functionalised GNPs, has been used to enhance anti-proliferative activity against K-562 cell lines compared to the free drug.[202] The GSH-mediated pathway has also been investigated to track the movement of GNPs carrying either fluorescein or doxorubicin molecules into a tumour model.[203]

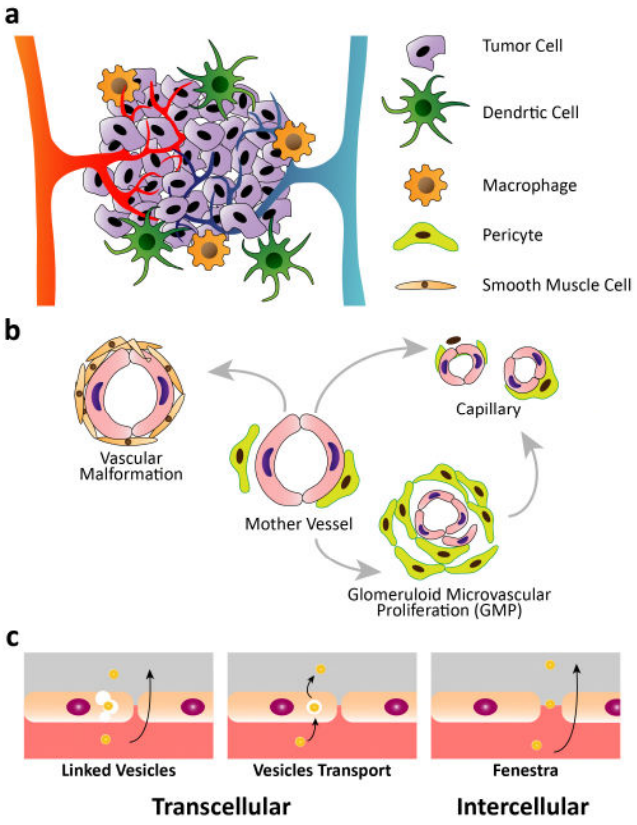


Fig. 5 (a) Schematic illustration of tumour microenvironment. (b) Mother vessels with thinned or compressed endothelial cells, degraded basement membranes, and pericyte detachment are highly permeable to both small molecules and proteins. Mother vessels can further differentiate into glomeruloid microvascular proliferations, vascular malformations, and capillaries. (c) Schematic representation of transcellular and intercellular transport of nanoparticles from across vessel wall.

Although, no GNPs have been approved clinically, a few of them have been going through clinical trials. These nanodrugs harness the light-absorbing ability of GNPs and are being currently explored for treating solid tumours and acne. One such gold colloid nanodrug approved for clinical trials is AuroLase, developed by Nanospectra, this comprises silica-gold nanoshells coated with polyethylene glycol (PEG) designed for the treatment of solid tumours by thermal ablation using a NIR source.[204] Here, silica provides a dielectric core, gold nanoshells confer thermal ablation ability, while the PEG induces an overall stability to the nanocomposite.[11] In another example, Sebashells developed by Sebacia Inc., which are similar to AuroLase, have been applied to treat acne by disrupting overactive sebaceous glands in the skin.[205] These Sebashells are topically administered to the site of acne, delivered deep into the sebaceous glands by low frequency ultrasound and ultimately stimulated via a NIR laser, utilising the heating capacity of the gold nanoshells for effective acne treatment (**Fig. 4 b and c**). These studies have been done *in vivo* showing the potential efficacy of Sebashells in preventing inflammatory acne lesions.[204]

Silver nanoparticles (AgNPs) possess anticancer and antitumour properties by inhibiting angiogenesis around tumour tissues. This has led to an extensive research regarding the potential application of AgNPs in cancer treatment both *in vitro* and *in vivo.* These studies have been conducted on different cancerous cell line models such as MCF-7, B10F17, A549, SiHa, and HeLa cell lines. Monomeric polymer encapsulated AgNPs have shown antileukemic properties against AML human cell lines.[206] This study provides a dose and size dependent response of AgNPs against these cell lines *in vitro.* AgNPs proved to be a potent antileukemic agent by providing high specificity against AML cell lines as opposed to normal hematopoietic cells. The mechanism behind this activity is that AgNPs increase the production of ROS and release of silver ions (Ag) from nanomaterials, this results in the induction of apoptosis and DNA damage. The release of Ag ions from AgNPs has also been proposed to induce tumour cell sensitisation,[207] these Ag ions are captured by free electrons, generating an oxidising agent which reduces the production of ATP in tumour cells and subsequently enhances intracellular ROS concentration. It has also been reported that release of Ag ions from AgNPs is greater as compared to bulk or powder silver.[208] Silver ions do not produce hydroxyl radicals (•OH) in the presence of H_2O_2, which is a mild reducing agent. In contrast, AgNPs produce •OH in the presence of H_2O_2 only at acidic pHs. This pH dependent •OH production by AgNPs confers their anticancer and antitumour activity. Biogenically synthesised AgNPS have also shown anticancer properties,[209] like AgNPs synthesised from mushroom which were tested against MDA-MB-231 human breast cancer cell lines. AgNPs disrupt the cell membrane integrity and increase production of lactate dehydrogenase (LDH), a biomarker for cell death. AgNPs synthesised using *Bacillus funiculus* and leaf extract from *Podophyllum hexandrum*, causes caspase mediated apoptotic cell death.[210,211] The antitumour activity of AgNPs was studied in multiple drug resistant (MDR) malignant melanoma cell tumours *in vivo.*[212] Here, transactivator of transcription (TAT) was anchored onto AgNPs surface; this conjugation increases the antitumour activity by several fold.

Cisplatin, a platinum complex, has been used for several decades for treating a number of abnormalities. In contrast, the application of platinum nanoparticles (PtNPs) as therapeutic agents is still in its infancy.[213] PtNPs possess the penetration capacity of entering cells[214] and the uptake and bioactivity of PtNPs have been investigated thoroughly which includes their cytotoxicity, genotoxicity, and effects on protein expression in human cells.[214] PtNPs penetrate into the cells through diffusion and are localised inside the cytoplasm. Upon exposure to PtNPs several events take place inside the cells such as, DNA damage at the S-phase of the cell cycle ultimately leading to apoptosis, up regulation of p53 and p21, and down regulation of proliferating cell nuclear antigens. These intracellular effects of PtNPs make it a potent anticancer therapeutic candidate for future use. *In vitro* PtNP treatment elicits DNA damage and antioxidant response.[142] The anti-cancer activity of platinum nanomaterials[215] has been shown in a recent study where synchronous application of PtNPs in conjunction with hadron therapy resulted in enhanced DNA strand disruption. Irradiation of platinum by carbon ion leads to the generation of •OH radicals which in turn amplifies the extent of damage to DNA.[216] An investigation with human colon carcinoma cells (HT29) exhibited a size-, dose-, and time-dependent response upon incubation with PtNPs.[142] The mechanistic reason behind the DNA damage was due to the release of Pt^{2+} ions from PtNPs causing a significant DNA damage and cellular apoptosis.[214,217] Hence, it was predicted that the nanoparticle itself does not interact directly with DNA, instead the soluble Pt^{2+} ions form a complex with DNA similar to cisplatin.[214] Culturing cells with PtNPs leads to the subsequent activation of p53 and p21, which causes genotoxic stress.[217] Thus, PtNPs can be potentially used in radiosensitisation as well.[215] Apart from being effective in cancer therapy, PtNPs have been applied for the treatment of Parkinson's disease by functioning as a mitochondrial complex I, by lowering ROS generation, and by scavenging free radicals such as superoxide and H_2O_2.[218] PtNPs synthesised using leaf extract have also been used to

treat Parkinson's disease.[219] The neuroprotective activity of the phytochemical conjugated PtNPs was studied in experimentally induced Parkinsonism in the zebra fish model. The results verified that upon pre-treatment with PtNPs, experimentally induced Parkinsonism could be reversed. PtNPs have been revealed to provide protection against oxidation-induced inflammation, this action of PtNPs decreases the osteoblastogenesis which causes bone loss.[220] PtNPs play an important role in reducing cellular oxidative stress by acting as a quencher for ROS such as H_2O_2 and superoxide, thus resembling two biological enzymes, catalase and superoxide dismutases (SOD). Apoferritin surface functionalised PtNPs (AF-PtNPs) have been applied for studying the scavenging capability of H_2O_2 and superoxide on mammalian cell line Caco-2. It was observed that AF-PtNPs successfully compensated H_2O_2 and superoxide. Owing to the receptor mediated internalisation of ferritin-functionalised nanoparticles into the cells, the membrane integrity was preserved and other adverse interactions with cellular proteins were avoided. After incorporation into Caco-2 cells, PtNPs decrease the oxidative stress within the cell and increase cell viability.[221] ROS scavenging and apoptotic properties of PtNPs have also shown promising potential in treating ultraviolet (UV) induced inflammatory responses in the skin.[222] An *in vitro* study in cell lines revealed a marked increase in ROS generation in UV-treated HaCaT keratinocytes cell lines, while a decrease in ROS production was observed in PtNPs treated cell lines. It was shown that mice treated with PtNPs gel prior to UV irradiation demonstrated a significant inhibition of UVB-induced inflammation and UVA-induced photo allergy compared to untreated controls.

Well documented studies on metal nanodrugs such as gold, silver and platinum have been thoroughly carried out for an extended period of time and some of them have even found their way into clinical trials (**Table 1&2**).[223] Technologies based on alternative noble metal nanocomposites are being intensively studied for probable applications in the medical sector. Palladium is one such noble metal and its nanostructure has drawn tremendous interest in the last decade for a variety of applications.[224–229] Despite the remarkable property of palladium as a metal and its diversified exploitation in several biomedical applications,[230,231] palladium nanocomposites have made a late entry into the nanobiotechnology field. Here, we discuss the therapeutic property of palladium nanomedicines routed in their catalytic, photothermal and biological activity. Firstly, polymer functionalised palladium resin has been used as a prodrug. This palladium nanocomposite resin complex has been shown to activate a number of biologically inert drugs such as 5-fluoro-1-propargyluracil[232] and N^4-propargyloxycarbonyl gemcitabine.[233] These two drugs are otherwise biologically inactive, but combined treatment with palladium nanocomposite resin restores the anti-proliferative and cytotoxic activity of these drugs in colorectal and pancreatic cancer cells. Toxicity of these resin palladium conjugates has been performed in the yolk sac of zebra fish and the results indicate no apparent toxicity while the chemical activity of the prodrug remains intact.[232] Photothermal efficiency of palladium nanostructures such as palladium nanosheets, has opened the door for their incorporation in cancer therapeutics. Hexagonal palladium nanosheets displayed efficient photothermal conversion efficiency due to their strong adsorption in the NIR region.[234] This photothermal efficiency depends on size and surface coating, which in turn affects the cellular uptake of these nanosheets.[235,236] An interesting finding is that palladium nanosheets tend to show better photostability than even gold and silver nanostructures. When palladium nanosheets are coated with GSH, they demonstrate better renal clearance.[237] *In vivo* studies have shown that in the absence of any irradiation, these GSH-palladium nanosheets exhibited longer retention time in the circulating blood, accumulate near the tumour site, and showed no toxicity, whereas upon irradiation with NIR laser, tumour ablation occurs.[237] The attractive properties of these nanostructured materials have further extended their application in more complex assemblies for combined photothermal-chemo/photothermal-photodynamic therapy treatment. Anti-cancer drug loaded silica nanoparticles entrapped within palladium nanosheets have proved to be an effective treatment strategy for combined photothermal and chemo-therapy; heat resulting from the NIR light conversion leads to pH dependent release of anti-cancer drugs and the cellular uptake of palladium nanosheets was significantly enhanced by the mesoporous coating of the silica nanoparticles.[238] Other lesser known nanomaterials of Rh, Ir, and Os have still not been put to wide use in biomedical research, although there have been a few examples. The UV plasmonic properties of Rh nanocomposites have been extensively studied to show their potential uses in UV plasmonic and photocatalytic applications.[239] Ir and Os nanoparticles remain less explored and need a thorough investigation regarding their future efficacy in clinical and human health research.

Table 1 Noble metal nanoparticles in clinical trials

Type of noble metal nanoparticles	Condition or disease	Properties of noble metal nanoparticles	NCT number	Phase	Recruitment Status
GNPs	Coronary Artery Disease Atherosclerosis	GNPs with silica-iron oxide shells with photothermic burning or melting effect onto the lesion	NCT01436123	Phase I	Terminated (under political pressure)
GNPs	Type 1 Diabetes	GNPs with attached peptide fragment related to insulin	NCT02837094	Phase I	Recruiting
GNPs	Gliosarcoma Recurrent Glioblastoma	Small GNPs with nucleic acid arranged on the surface (NU-0129)	NCT03020017	Phase I	Active, not recruiting
GNPs	Stable Angina Heart Failure Atherosclerosis Multivessel Coronary Artery Disease	GNPs with silica-iron oxide shells with photothermic burning or melting effect onto the lesion	NCT01270139	N/A	Completed
GNPs/AgNPs	Caries Class Ii	AgNPs & GNPs suspended in 70 % isopropyl alcohol used for cavity pre-treatment	NCT03669224	N/A	Not yet recruiting

GNPs	Pulmonary Hypertension	GNPs coated with organic ligands as sensor array for detecting volatile organic compounds in exhaled breath in patients	NCT02782026	N/A	Unknown
GNPs	Stomach Diseases	Functionalised GNPs & carbon nanotubes nanosensors array identifying gastric diseases	NCT01420588	N/A	Unknown
GNPs	Parkinson's Disease	Functionalised GNPs & carbon nanotubes nanosensors array identifying Parkinson's diseases	NCT01246336	N/A	Completed
AgNPs	Foot Infection Fungal Infection, Bacterial	AgNPs containing cream	NCT03752424	Phase I	Recruiting
AgNPs	Oral microbial colony formation	AgNPs containing gel	NCT02761525	N/A	Completed
AgNPs	Dental Caries	Nanosilver fluoride (5%) solution	NCT01950546	Phase I	Completed
AgNPs	Tooth Demineralization	AgNPs incorporated into the primer orthodontic Transbond XT	NCT02400957	Phase III	Unknown
AgNPs	Chronic Rhinosinusitis	Colloidal AgNPs	NCT03243201	Phase I	Withdrawn (IND not approved)
AgNPs	Down Syndrome	AgNPs containing fluor varnish	NCT01975545	Phase II	Unknown
AgNPs	Partial Dentin Caries Removal	Nanosilver fluoride solution	NCT03193606	N/A	Active, not recruiting
AgNPs	Central Venous Catheter Related Infections	Central venous catheter impregnated with AgNPs (AgTive®)	NCT00337714	Phase IV	Completed
AgNPs	Antimicrobial efficacy In healthy subjects	Nanosilver gel	NCT00659204	Phase III	Unknown
AgNPs	Rhinosinusitis	Topical silver colloid	NCT02403479	Phase I/II	Unknown
AgNPs	Postoperative Pain	AgNPs gel	NCT03692286	Phase IV	Not yet recruiting
AgNPs	Dental Caries	Nanosilver fluoride solution	NCT03186261	Phase III	Not yet recruiting
AgNPs	Plantar Warts	Colloid silver and fig extract mixture	NCT02338336	Phase I/II	Completed
AgNPs	Surgical Site Infection	Colloid silver containing bath wipes	NCT03401749	Phase IV	Recruiting

Exploring the anti-viral potential of NMN: Concern regarding growing microbial resistance to all types of antimicrobial agents used against different infectious diseases has led to a fusion between nanotechnology and microbiology. Broad-spectrum activities of noble metal nanostructures and their application to resolve microbial resistance issues have initiated a positive development in this field. The antibacterial, antifungal, antiviral, and antiprotozoal property of noble metal nanoparticles have attracted huge interest from the scientific community throughout the world (**Fig. 6**). This section will elucidate some of these diversified and multifunctional facets of noble metal nanoparticles with regards to their antimicrobial potentials (**Table 3**). Apart from their roles as antitumour agents, GNPs have been employed to deliver antibiotics and antibacterial agents as well. A variety of antibiotic conjugated gold colloids have shown promising activity against various bacterial strains.[240] The exact mechanism behind this antibacterial activity of GNPs has evaded researchers, but one of the primary reasons could be stable antibiotic-GNP conjugate formation. In one report it has been suggested that the direct use of antibiotic in the synthesis of GNPs offers a much-improved antibacterial activity.[241] GNPs are also investigated for their antiviral activity against human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS). Functionalisation of GNPs with HIV-1 integral protein transduction domain (PTD) was tested *in vitro* in a human fibroblast cell line. It was observed that surface modified GNPs (~5 nm) can traverse across the plasma membrane, whereas larger particles (~30 nm) are unable to do so. This study provides clear evidence that smaller sized GNPs can be used as a drug delivery vehicle for AIDS.[242] Free SDC-1721, a derivative of TAK-779 and a known CCr5 antagonist, which is the primary entry co-receptor for transmitted strains of HIV-1, has no inhibitory effect on HIV infection. However, when conjugated with GNPs, the resulting SDC-1721-GNPs conjugates showed enhanced inhibitory activity against HIV infection.[243] Another anti-HIV activity was studied with bare and PEG coated GNPs, in which it was demonstrated that bare GNPs exhibit significant anti-HIV properties as compared to PEG-GNPs; this may be due to the fact that nanoparticles coated with charge stabilisers (PEG) are larger in size and hence cannot enter into the cells and inhibit viral growth.[244] Receptor binding inhibitory activity of GNPs against HIV was studied using sugar coated nanoparticles. This study showed that sugar coated GNPs block the function of dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN), which constitutes a major receptor for HIV-1.[245] GNPs have also been applied for treatment of Tuberculosis (TB) by utilising multi-block copolymer conjugated GNPs as a successful delivery vehicle for TB drugs such as Rifampicin.[246] Application of GNPs as a drug delivery machinery has led to their incorporation in immunisation therapy due to their small size and ability to enter cells. For example, GNP-conjugated chitosan exhibits an enhanced serum antibody response which is several folds more powerful than the naked DNA vaccine.[247] GNPs are potential carriers for the development of synthetic peptide vaccine against foot-and-mouth disease virus (FMDV). A synthetic peptide resembling FMDV proteins was conjugated with GNPs, and after immunisation it was observed that there was production of specific antibodies against the peptide.[248] The role of GNPs in cancer immunotherapy has also been studied extensively.[249] There are

several reviews regarding the advancements of conjugated GNPs in vaccine delivery.[250] One group of researchers illustrated the adjuvant properties of GNPs in facilitating the delivery of both the ovalbumin (OVA) peptide antigen and CpG adjuvant, resulting in an enhanced therapeutic effect in a B16-OVA tumour model.[251] Silver nanoparticles (AgNPs) represent one of the most common nanocomposites used in consumer goods and in medical products, including wound healing bandages and a variety of antiseptic sprays.[252] AgNPs have been shown to provide protection against various infectious diseases, since they act as antifungal, antiarthropod, antiviral and antiprotozoal agents.[253] Additionally, the powerful antimicrobial as well as highly toxic activity of silver nanocomposites have been extensively studied and reported.[252,254–257] AgNPs have been shown to possess higher cytotoxicity compared to the well documented GNPs.[258–260] Three probable explanations are given in order to describe the antibacterial activity of AgNPs: (i) direct interaction of AgNPs with the bacterial cell membrane results in membrane disruption and complex formation with substances located intracellularly;[261] (ii) AgNPs interact with the thiol groups (-SH) and produce ROS;[262] and (iii) subsequently, there is release of Ag^+ ions which inhibit respiratory enzymes and also increase ROS generation **(Fig. 7)**.[263]

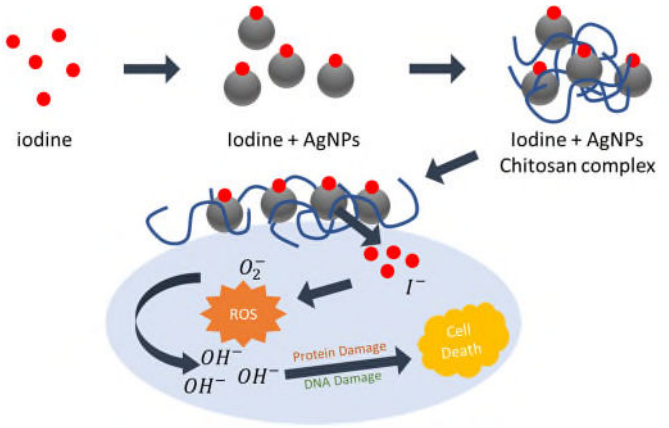


Fig. 6 Schematic representation of the proposed mechanism of antibacterial activity of the iodinated chitosan-Ag NP composite. Modified from Ref [262].

Table 2 Therapeutic applications of noble metal nanoparticles.

Type of noble metal nanoparticles	Application	Properties of noble metal nanoparticles	References
GNPs	Inhibition of $VEGF_{165}$ and bFGF	Anti-angiogenic	155–157
GNPs	Prevention of multiple myeloma	Anti-angiogenic	160
GNPs	Inhibition of B-chronic lymphocytic leukemia	Anti-angiogenic	264
GNPs	Prevention of collagen-induced arthritis	Anti-angiogenic	265
GNPs	As PDT agents for cancer treatment	LSPR	199,204,266
GNPs	As PTT agents for cancer treatment	LSPR	171,186–188
Gold nanorods	As PDT therapy for cancer treatment	LSPR	172–174
GNPs	For skin cancer treatment	LSPR/hyperthermia	174,204,205
GNPs	Treatment for liver cancer	LSPR/Radio frequency ablation	175
AgNPs	Inhibition of VEGF	Anti-angiogenic	161,162
AgNPs	Cancer treatment	Anti-angiogenic	206,207
AgNPs	Breast cancer treatment	Anti-angiogenic	209–211
AgNPs	Prevention against MDR malignant melanoma cell tumours	Anti-angiogenic	212
PtNPs	Cancer treatment	LSPR/radiation therapy	215
PtNPs	Cancer treatment	Anti-angiogenic	214,217
PdNPs	Cancer treatment	Anti-angiogenic	232,233
PdNPs	As PTT agents for cancer treatment	LSPR/Hyperthermia	234–236
PdNPs	Tumour treatment	LSPR/Photothermal ablation	237

Table 3 Antimicrobial properties of noble metal nanoparticles.

Type of noble metal nanoparticles	Application	Antimicrobial properties	References
GNPs	Inhibition of vancomycin-resistant enterococci	Antibacterial	240
Cefaclor capped GNPs	Inhibition of *E. coli* and *S. aureus*	Antibacterial	241
GNPs functionalised with PTD	Prevention of HIV-1	Antiviral	242
GNPs-SDC 1721 conjugate	Inhibition of HIV-1	Antiviral	243
PEG-GNPs	Prevention of HIV	Antiviral	244
Sugar coated GNPs	Inhibition of receptor binding in HIV-1	Antiviral	245
Copolymer conjugated GNPs	As drug delivery vehicle for Rifampicin for treatment of Tuberculosis	Antibacterial	246
AgNPs	Inhibition of *S. aureus, Streptococcus pyrogenes, S. enteric* and *Enterococcus faecalis*	Antibacterial	267

PEG-AgNPs	Inhibitory action against *S. aureus, Salmonella typhimurium*	Antibacterial	268
AgNPs	Prevention of Tuberculosis	Antibacterial	269
AgNPs	Inhibitory action against *Candida albicans, C. Tropicalis, Trichophyton mentaprophytes, C. glabrata* and *C. krusei*	Antifungal	253,270
AgNPs	Prevention of severe keratitis	Antifungal	271
AgNPs	Inhibition of plaque formation in MPV	Antiviral	272
AgNPs	Prevention of HIV	Antiviral	273–277
AgNPs	Inhibition of virus binding in HIV-1	Antiviral	275
AgNPs	Prevention of H1N1	Antiviral	278
AgNPs	Inhibitory action against HSV-1, HSV-2 and HPIV-3	Antiviral	279,280
AgNPs	Cytotoxic effect against AD3 virus particles	Antiviral	281
Polysaccharide coated AgNPs	Inhibition of TCRV	Antiviral	282
AgNPs	Inhibitory action against *Cryptosporidium parvum* in water purification	Antiprotozoal	283,284
AgNPs	Prevention of leishmania	Antiprotozoal	284,285
AgNPs	Inhibitory action against *Plasmodium falciparum*	Antiprotozoal	286,287
AgNPs	Wound healing	Antibacterial and Antifungal	288–290
PtNPs	Prevention of Parkinson's disease	Antioxidant	218,219
PtNPs	Prevention of bone loss	Antioxidant	220
PtNPs and AF-PtNPs	ROS scavenger	Antioxidant	221
PtNPs	Prevention of UV-induced inflammatory responses in skin	Antioxidant	222
PtNPs	Inhibitory activity against *P. aeruginosa*	Antibacterial	291
Ru nanoparticles	Inhibition of Gram-positive and Gram-negative bacteria	Antibacterial	292

Mycosynthesised AgNPs using different strains of fungi have shown significant efficacy against *Staphylococcus aureus, Streptococcus pyrogenes, Salmonella enteric* and *Enterococcus faecalis.*[267] AgNPs associated with traditional antimicrobial drugs have been deployed to provide the possibility of more rational therapies. AgNPs synthesised using *Aspergillus flavus* and upon conjugation with several antibiotics such as ciprofloxacin, gentamicin, vancomycin and trimethoprim have been studied.[293] When AgNPs were used in combination with gentamicin, ampicillin, vancomycin, and oflaxacin, there was an improvement in antimicrobial activities. This enhancing effect of AgNPs emphasises the potency of Ag in increasing the membrane permeability.[294] One of the reports suggests that AgNPs enter the cell by disrupting the cell membrane and interfering with the cytoplasmic content.[295] The size-dependent antibacterial activity of AgNPs has been investigated and it has been indicated that smaller AgNPs exhibit enhanced antibacterial activity as a result of relative increase in contact surface area.[296] PEG-AgNPs of different sizes were tested for their antibacterial activities against Gram-positive (*S. aureus*) and Gram-negative (*Salmonella typhimurium*) bacteria, the results demonstrated that size modulation of PEG-AgNPs can significantly enhance the antimicrobial properties of AgNPs against both these pathogens.[268] There are several reports which throw light on the antibacterial activity of AgNPs against MDR.[269] It has been demonstrated that AgNPs and GNPs are equally effective against *E. coli* and *Mycobacterium tuberculosis* (MTB), but a higher antimicrobial activity has been reported by AgNPs. This result suggests that AgNPs can be used for TB therapies. In consistency with the above observation, it has been established that AgNPs coated with bovine serum albumin (BSA) offer better biocompatibility against TB without losing their effectiveness, as opposed to polyvinyl pyrrolidone (PVP)-AgNPs.

The antifungal property of colloidal silver is comparatively less studied in comparison to its antibacterial activity. Still, there are numerous reports which confirm that AgNPs can be a potent antifungal agent. AgNPs have shown significant activities against different fungal species such as *Candida albicans, C. tropicalis, Trichophyton mentagrophytes, C. glabrata* and *C. krusei.*[269] Biosynthesised AgNPs seem to have antifungal properties against *Phoma glomerata, P. herbarum, Fusarium semitectum,* and *Trichoderma species;* they also showed synergistic effect when in conjugation with a standard antifungal agent such as fluconazole.[270] Antifungal action of AgNPs in combination with heterocyclic compounds, namely thiazolidine, phthalazine, pyrazolo, and hydrazide, were investigated against *Aspergillus flavus* and *C. albicans.* The results indicate an enhanced antifungal activity in combination with above mentioned compounds as compared to heterocycles alone.[297] In a separate study, AgNPs and natamycin were tested against various strains of fungi among patients suffering from severe keratitis and the authors observed a higher antifungal activity of AgNPs in comparison to natamycin.[271] A possible explanation for the antifungal properties of AgNPs might be due to its role in disrupting cell membrane integrity and by inhibiting the normal budding process in yeasts.[298] AgNPs are also emerging as one of the possible potent options for managing viral diseases due to their potential antiviral properties.[299] AgNPs are capable of acting on broad range of viruses and offer a lower probability of developing resistance against viruses as compared to conventional antivirals. AgNPs synthesised by biological processes tends to exhibit higher antiviral properties as compared to chemically synthesised particles.[279,300] Kidney epithelial cells extracted from an African green monkey and co-incubated with AgNPs displayed significantly reduced plaque formation with Monkeypox virus (MPV).[272] The

preventive antiviral nature of AgNPs has been extended to HIV, where they are seen to prevent the host cells from binding with the virus *in vitro*.[273,274] AgNPs effectively decrease HIV-1's infectivity by acting directly on the virus by binding to the glycoprotein gp120.[275] This structural alteration in turn, decreases the CD4-dependent virion affinity, thereby preventing HIV-1 infection.[275] Recent studies have yielded promising results regarding the antiviral property of AgNPs against influenza A H1N1 virus.[278] The antiviral potency of AgNPs has been further demostrated against *Herpes simplex* virus types 1 and 2 (HSV-1 and HSV-2) and human parainfluenza virus types-3 (HPIV-3) in a dose-dependent manner.[279] A similar study was carried out against adenovirus type 3 (AD3) where it was illustrated that AgNPs processed cytotoxic effect against AD3 by not only damaging the virus particles, but also disrupting the DNA structure. In addition, AgNPs can damage the capsid protein which inhibits the virus attachment to the host.[281] Capping agents play a significant role in reducing infectivity and enhancing biological compatibility. AgNPs coated with stabilising agents such as PVP, PEG, and citrate have also been proved to be powerful antiviral agents, in a size-dependent manner. It has been shown that a polysaccharide coating on AgNPs protects the cell from the toxic effect of the nanoparticles, but also reduces the NP's activity against tacaribe virus (TCRV).[282] In contrast, the same capping agent results in better antiviral activity efficiency against MPV.[272] Other examples of coated AgNPs as effective antiviral agents have been offered in several studies such as HIV-1,[275–277] HSV,[280] and respiratory syncytial virus (RSV).[301] PVP capped AgNPs have been used to prevent transmission of HIV-1 infection using an *in vitro* human cervical tissue-based organ culture[275] and also as a coating for polyurethane condoms in order to inactivate infectious microorganisms.[280]

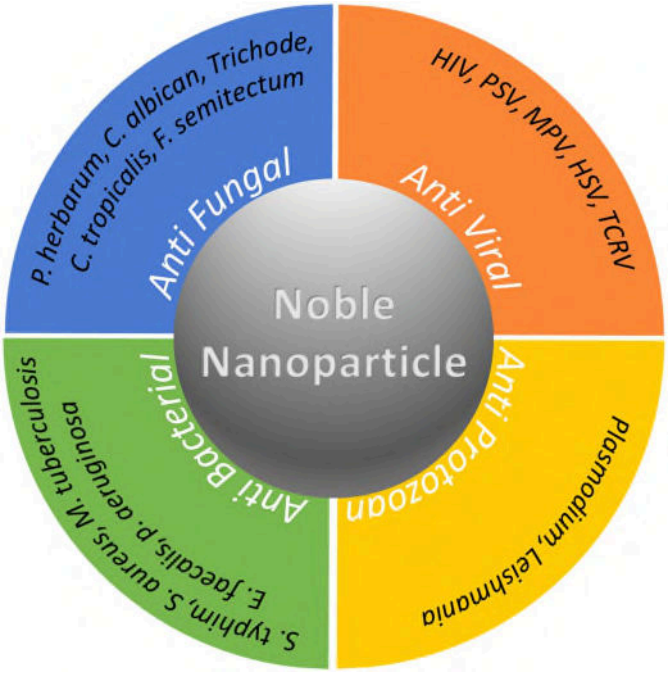


Fig. 7 Schematic diagram of anti-infective properties of NMN.

The studies showed effective reduction in HIV infection, but the mode of action is yet to be ascertained. One possible mechanism suggested is that AgNPs interact directly with surface glycoproteins and thereby interfere with the binding and fusion events during viral penetration into susceptible cells. Additionally, AgNPs are also able to inhibit post-entry stages of the HIV-1 life cycle by blocking various functional HIV-1 proteins or reducing the rate of proviral transcription by binding to the RNA or DNA moieties. The antiprotozoal activity of AgNPs has also been studied recently. The efficacy of AgNPs as an antiprotozoal agent against *Cryptosporidium parvum* was assessed and the disinfectant properties of AgNPs for water purification was demonstrated.[283,284] Green-synthesised AgNPs using *F. oxysporum* have shown promising result against *Leishmania amazonesis* promastigotes both *in vitro* and *in vivo*.[284] AgNPs inhibit the biological activity of *Leishmania tropica* and this effect was enhanced under UV irradiation. The enhancement in anti-leishmanial activity under UV light was attributed to the ability of AgNPs to release Ag^+ ions, leading to the interaction of the AgNPs with the parasitic surface lipophosphoglycan and glycoproteins, which are responsible for spreading infection.[285] AgNPs have profound influence against plasmodia, biosynthesised AgNPs using Acanthaceae and leaf extract of *Catharanthus roseus* have demonstrated promising indication against *Plasmodium falciparum* in a size-dependent study.[286,287] Wound healing promoted by AgNPs provides possible direction of research. Topical application of AgNPs in a mice model exhibited wound healing and reduced scar formation properties in a dose-dependent manner.[288] When it was used for burns, AgNPs of <20 nm in diameter at very low concentrations were able to work simultaneously as an antimicrobial as well as an anti-suppressant against local systematic inflammation *in vivo.* Studies of AgNPs acting as skin wound-healing agents *in vivo* have been. It was observed that low concentrations of AgNPs (~10 nm) promoted wound closure and wound contraction by enhancing the proliferation and differentiation of keratinocytes and fibroblasts.[289] Another study concerning the skin penetration efficacy of colloidal silver and silver nanoclusters has shown that they are able to penetrate into human stratum corneum as well as the outermost surface of the epidermis.[290] Polymer conjugated AgNPs in the size range of <50 nm can promote penetration through intact as well as damaged human skin; these future applications of AgNPs could have relatively long-lasting therapeutic benefits.

Studies on the antibacterial property of PtNPs performed with the pathogen, *P. aeruginosa*, observed that PtNPs showed size-dependent bacterio-toxic and bacterio-compatible properties.[291] Ruthenium (Ru), rhodium (Rh), iridium (Ir) and osmium (Os) are the other so-called noble metals; they have gained considerable importance in the drug industry owing to their anticancer, antirheumatic, antimalarial, and antibacterial activities. Their assimilation into nanobiotechnology research is not as mature as other well-known nanomaterials such as gold, silver, platinum, and palladium. Ru is a 4d transition metal belonging to the platinum group.[302,303] Despite the limited use of Ru nanoparticles in biomedical and clinical research, they have impacted on several other important application areas including catalytic dehydrogenation,[304] methanol fuel cells,[305] synthesis of diesel fuels,[306] degradation of azo dye,[307] and removal of organic pollutants from water,[308] to name but a few. Recently, one group showed the antibacterial activity of Ru nanoparticles.[292] In this study, they synthesised Ru nanoparticles using leaf extract; green-synthesised Ru nanoparticles, in the size range of ~40 nm, were tested against gram-negative and gram-positive bacteria in order to determine their antibacterial efficacy. The results obtained demonstrated that Ru nanostructures tend to be most effective against gram-positive bacteria. Ru nanoparticles attach themselves onto the bacterial membrane by electrostatic and coordinated covalent interactions, leading to generation of ROS within the bacterial cell and subsequent ultimate cell death.[239] Hence, we could see Ru nanoparticles being applied for development of drugs against gram positive bacterial diseases.

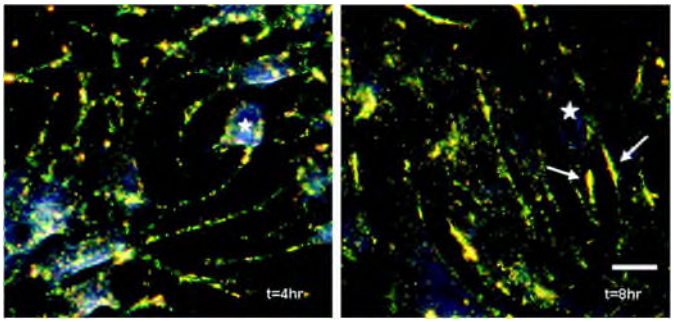


Fig. 8 The arrangement of actin is followed as cells spread on a monolayer of collagen IV. Time points at 4 h (left) and 8 h (right) are shown. White stars indicate a cell body and arrows indicate actin alignment. Scale bar is 20 µm. Reprinted with permission from[139]

Diagnostic and imaging potential of NMN

Diagnosis and sensing applicability of NMN: The phenomenon of Localised Surface Plasmon Resonance (LSPR) in noble metal nanoparticles has been most widely used for the development of new biosensors. LSPR arises from the electromagnetic waves that travel along the surface of conductive metals and semiconductors.[309] Upon excitation with an external light source, noble metal nanoparticles produce an intense absorption and scattering as a result of the collective oscillation of the conductive electrons present at their surface and conductive bands. Noble metals, especially gold and silver, have been employed in many biosensors.

Table 4 Diagnostic application of noble metal nanoparticles.

Type of noble metal nanoparticles	Application	References
GNPs	Detection of DNA	310–315
GNPs	Detection of SNPs, UV-induced mutagenic or carcinogenic DNA dimmers and detection of unamplified hepatitis C virus RNA	316–319
Citrate capped GNPs	Sensing of thiourea and melamine	320,321
Fibrinogen functionalised GNPs	Detection of genes associated with sickle-cell anaemia	313
Gold nanobeacons	Mutation associated with cystic fibrosis	322,323
GNPs	Detection of HIV-1 p24 antigen	324,325
GNPs	Detection of HBV genes	326
GNPs	Detection of *Mycobacterium tuberculosis* DNA sequence	327–329
GNPs	Biomarkers for Alzheimer's disease	330
Graphene oxide-GNPs	Detection of MB	331
GNPs	Quantification of NAADP	332
AgNPs	Detection of bombesin, a neurotransmitter tumour marker	333
AgNPs	Sensing protein-protein and protein-small molecule interaction	334,335
AgNPs	Glucose detection	336,337
AgNPs	Detection of DNA	338
Peptide functionalised GNPs	Anthrax biomarker detection	339
GNPs/AgNPs	Detection of DNA sequence for HIV	340–343
GNPs-MBA conjugate	Hepatitis B virus antigen	344
Gold nanobeacons	Detection of erbB-2 and ki-67 breast cancer biomarkers	345
Graphene oxide-PtNPs	Detection of cancer cells	346,347
GNPs	Detection of *E. coli*	348
GNPs modified with 4-amino-1-(-3-mercapto-propyl)-pyridine hexafluorophosphate	Sensing human IgG concentration	349
Graphene oxide-GNPs	Detection of alpha-fetoprotein	350
PdNPs	Detection of alpha-fetoprotein	351
PdNPs	Detection of prostate specific antigen	352
AgNPs-titanium phosphate	Immunodetection of IL-6	353
Graphene oxide-AgNPs	Immunodetection of *E. coli*	354
6-ferrocenyl hexanethiol functionalised GNPs	Immunosensing of prostate specific antigen	355

LSPR leads to exceptionally high absorption and scattering properties within the UV-visible wavelength which confers the particles with higher sensitivity in comparison to conventional organic dyes, making them a perfect foil for colorimetric sensor applications.[356,357] The sensing efficiency of GNPs depends upon their intrinsic localised surface plasmon resonance, with wavelengths around 510-530 nm for gold nano formulations of around 4-40 nm, which can be used for biosensing.[358] This effect is generally absent in the individual atoms and the bulk form.[359,360] The binding of molecules onto the particle surface changes the LSPR, which is reflected by the scattered light in dark field microscopy.[361] In addition, SPR is drastically changed when the average distance between the Au particles changes during the formation of gold colloid aggregates.[362] This attribute of GNPs has been utilised, for example, for the detection of DNA,[310,311] by taking advantage of the binding affinity of single and ds-DNA onto their surface. Complementary charged GNPs interact electrostatically with the free bases of single stranded (ss)-DNA, which in turn provides colloidal stability to the nanoparticles in the presence of high salt

concentrations. In contrast, dsDNA molecules adsorb less to the GNPs surface and hence are unable to provide colloidal stability under increasing ionic strength, leading to aggregation of GNPs, which results in LSPR and colour change simultaneously. GNPs conjugated with oligonucleotides that are complementary to the target sequence appear as a red solution in the absence of the target sequence, whereas in the presence of the target, hybridisation occurs and the solution changes to violet/blue due to LSPR.[312] This approach has been successfully deployed for the detection of single nucleotide polymorphism (SNPs), UV induced mutagenic or carcinogenic DNA dimmers, and in the detection of unamplified hepatitis C virus RNA isolated from clinical specimens.[316–319] Citrate capped GNPs and AgNPs have been investigated for sensing thiourea and melamine using a colorimetric assay system.[320,321] In this method, the presence of thiourea and melamine significantly reduces the overall surface charge of GNPs leading to their aggregation and this in turn is detected colorimetrically indicating the concentration of thiourea and melamine present. Detection of DNA, aptamers, and oligonucleotides has received considerable attention in recent years because it has important implications in medical diagnostic, food safety monitoring, and the drug industry. Many studies have been conducted using surface functionalised GNPs for the detection of DNA, aptamers, and oligonucleotides.[313–315] GNPs functionalised with thiol (–SH) modified ssDNA probes have been used to detect a single mismatch through a cross-linking approach in the presence of a complementary ssDNA.[363,311] A non-cross-linking approach was used for the specific detection of genes associated with sickle-cell anaemia using fibrinogen functionalised GNPs and a thrombin binding aptamer.[313] Fluorescence-based noble metal nanoparticle biosensors have been developed by utilising the quenching property of these nanomaterials. This is not to be confused with plasmonic nanoparticles, where the surface electrons can couple with electromagnetic waves with wavelength much larger than the size of the particles. Two approaches have been used so far: (i) molecular nano-beacons, where noble metal nanoparticles are surface conjugated with fluorescent-labelled ssDNA which forms a hair-pin loop like structure; and (ii) noble metal nano-probes, which consist of noble metal nanoparticles functionalised with ssDNA that hybridise with another fluorescent-labelled ssDNA probe. Molecular nano-beacons have been used to detect single-base mismatches in DNA with a higher sensitivity as compared to conventional molecular beacons.[322] In another example, nano-beacons based on 13 nm GNPs have been successfully used to detect mutation associated with cystic fibrosis.[323] In all these cases, the loop forming structure of the nano-beacon brings the fluorescent dye moiety in close proximity to the noble metal nanoparticle's surface resulting in quenching of the fluorescence intensity of the fluorophore. In the presence of a complementary DNA/RNA target, the hairpin structure is disrupted by hybridisation and restores the fluorescence of the labelled strands. A gold nanorods containing gelatin hydrogel is developed for rapid recognition of circulating tumour cells (**Fig. 9**). An innovative "chemical nose" technique has been developed using conjugates of GNPs and fluorophore which provides high sensitivity sensing of biomolecular targets (**Fig. 10**).[364–366] This method was used for rapid and accurate differentiation between normal, cancerous, and metastatic cells.[367] Appropriately functionalised gold nanoparticles can be used for a simple colorimetric test for small concentrations of aqueous heavy metal ions, which includes toxic heavy metals such as lead, cadmium and mercury. GNPs are aggregated in the solution in presence of divalent metal ions by ion-templated chelation process.[368] The development of a fast and reliable method for glucose sensing is a prerequisite for the treatment and control of diabetes.[369,370] Most electrochemical methods use enzymes such as glucose oxidase or glucose dehydrogenase to catalyses the specific oxidation of glucose. GNPs entrapped in a silica network can enhance the non-enzymatic oxidation of glucose providing one possible alternative to the use of enzyme electrodes under appropriate circumstances.[371] A sandwich interface containing chitosan/Au nanoparticles/glucose oxidase multilayer on platinum electrodes has been claimed to provide high sensitivity and a low detection limit for glucose, presumably due to the high electrochemically active surface area and diffusion characteristics of GNPs at the sandwich interface.[372]

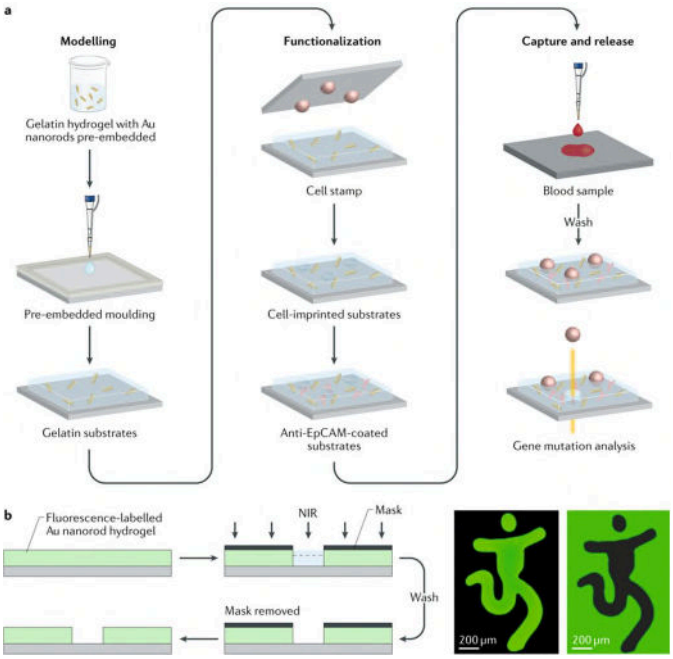


Fig. 9 (a) Near-infrared (NIR)-responsive cell-imprinted gelatin for capture and photothermal selective release of single circulating tumour cells (CTCs) from peripheral blood. The cell-imprinted substrate is fabricated by imprinting target cancer cells on a Au nanorod-embedded gelatin hydrogel. CTCs are then separated by anti-epithelial cell adhesion molecule (anti-EpCAM)-modified cell-imprinted gelatin. This is followed by selective site release of an individual cell by exposure to a cell-sized NIR laser spot. (b) Schematic showing the selective photodegradation of the thermoresponsive gel doped with Au nanorods. Fluorescence microscope image of the fluorescein isothiocyanate (FITC) gelatin with a mask on top (bottom left). Fluorescence microscope image of the FITC gelatin without the mask and after removal of the gel degraded via selected NIR irradiation (bottom right). Reprinted with permission from [373]

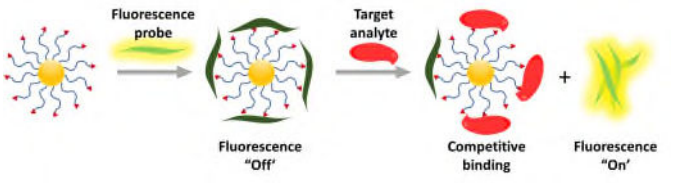


Fig. 10 Scheme illustration of GNP-based chemical nose for sensing of biomolecules based on competitive binding and fluorescence quenching. Modified from ref[364]

Antibody conjugated GNPs have been used for biological staining in electron microscopy and for radioactive labelling *in vivo*. The application of gold colloids in bio-diagnostics over conventional organic dyes and quantum dots offers a number of advantages which include reduced toxicity and contrast enhancing agents for imaging. Gold nano formulations can provide signal enhancement to standard enzyme-linked immunosorbent assays (ELISAs), such as immunochromatographic test strips where both primary and secondary antibodies are attached to GNPs.[374] Surface modification of GNPs with Cy5-antibody as a fluorescence probe could replace the

conventional ELISA assay, since this technique does not require a secondary antibody and offers high sensitivity.[375] Gold nanoshells are capable of detecting nanogram quantities of various analytes present in whole-blood in chemiluminescent analysis of antibodies. This technique is far superior to ELISA in terms of technical proficiency.[376] The intense light scattering by large GNPs makes them a potent probe for cancer detection. Immuno-targeting of antibody-GNPs to label cancer cells is achieved by conjugating them with antigens overexpressed in cancer cells. For example, cervical epithelial cancer cells (SiHa cells), which overexpress the transmembrane glycoprotein, epithelial growth factor receptor (EGFR), were successfully detected by immune-targeted gold colloids.[377] GNPs nanoprobes have also potentially simplified diagnosis of cancer by detecting SNPs and mutation.[378,379] A new approach has been added in the already existing repertoire of GNPs in the diagnosis of cancer, wherein a combined solid-phase microextraction with gas chromatography/mass spectrometry has been employed for the identification of volatile organic compounds acting as biomarkers for lung cancer.[380]

Gold colloid bio-barcode amplification assays (BCA) can detect HIV-1 p24 antigen at very low concentration levels (0.1 pg/mL). The conventional detection limit with ELISA is reported as 1-15 pg/mL,[324] while using GNPs there was a 100 to 150-fold enhancement in the detection limit.[325] Another, technique for reliable and sensitive method for HIV-1 virus is based on gold colloid labelled silver staining in conjunction with polymerase chain reaction (PCR). The results demonstrated the highly sensitive and accurate potential for HIV-1 diagnosis using GNPs.[381] Functionalisation of gold colloids with Hepatitis B virus (HBV) DNA gene probes could be used to detect HBV DNA directly. This fluorescence-based method was highly sensitive and cost effective and could in future replace the highly complex multi-gene detection chips.[326] Diagnostic applications of gold nano-formulation probes have found their way into tuberculosis detection also. A target oligonucleotides sequence, suitable for mycobacteria identification was used here. At high ionic strength, aggregation of the nanoprobe takes place in the absence of any complementary DNA sequence specific to target oligonucleotides and turns the solution purple. On specific probe hybridisation to a complementary sequence (i.e. DNA from *Mycobacterium tuberculosis*), no aggregation of GNP nanoprobe occurs and the solution remains red.[327] GNPs have been applied for the diagnosis of Alzheimer's disease biomarkers based on the SPR property of gold colloids. Here, gold nanoparticles are used to monitor the interaction between the antigen, amyloid-β derived diffusible ligands (ADDLs) and specific anti-ADDL antibodies.[330]

GNPs have been used as nanoprobes for detection and differentiation of *Mycobacterium tuberculosis* (MB) from other members of *M. tuberculosis* complex (MBC). In one report, oligonucleotide modified GNPs were developed as a selective nanoprobe for DNA-based detection and differentiation of MB and MBC. The technique was highly selective for distinguishing between MB and MBC.[328] In yet another approach, *Mycobacterium bovis* and MBC were successfully differentiated by GNP nanoprobes.[329] A new DNA-based biosensor for the highly sensitive detection of the specific IS6110 DNA sequence of MB has been achieved by using reduced graphene oxide-GNPs as a sensing platform and GNPs-polyaniline as a label for signal amplification.[331] The nanoprobing activity of GNPs for sensing MB shows potential for use in clinical diagnostics. Noble metal nanoparticles have been used for enhancement of Raman signals in Surface-Enhanced Raman Scattering (SERS) for different types of analytes, and this has led to a wide variety of biosensors for the detection of nucleic acids, antibodies, proteins, and other biological molecules.[382,383] Raman scattering arises from the inelastic scattering of photons that hit the analyte molecule in such a way that energy is either gained or lost so that the scattered photons are shifted in frequency. This interaction generates a narrow spectrum of bands unique for each analyte, and this signal is greatly enhanced in presence of noble metal nanoparticles by an order of 10^5 to 10^6 than the respective non-SERS Raman signals.[384] This enhancement is mainly attributed to the LSPR properties of the noble metal nanostructures.[385] A label-free SERS biosensor has been developed based on a glass surface coated with a layer of GNPs to detect and quantify nicotinic acid adenine dinucleotide phosphate (NAADP), which plays a crucial role in intracellular Ca^{2+} release.[332] This label-free SERS system allowed for a rapid detection of NAADP, making it a valuable tool for the study of normal and cancerous cells. In a similar approach, a surface covered with AgNPs were used instead of GNPs to detect bombesin, a neurotransmitter tumour marker and its analogues by SERS.[333] This research group has also developed a protocol to monitor protein-protein and protein-small molecules interaction using AgNPs staining of the samples for producing active substrates for SERS.[334,335] Another group of researchers used SERS to detect glucose levels by employing a self-assembled monolayer of decanethiol over an aggregated AgNPs film to increase glucose adsorption, which is otherwise minimal for bare-SERS substrates.[336,337] SERS has also been used for detecting ssDNA by applying a slide derivatised with uncharged peptide nucleic acids which recognise and hybridise with specific, negatively charged ssDNA. This system mediated the adsorption of positively charged AgNPs upon hybridisation.[338] The use of functionalised noble metal nanoparticles has been investigated for a more versatile and specific SERS-based sensing of biomolecules. In this method, SERS signals were generated by using a probe (DNA, antibody) functionalised noble metal nanoparticles and a Raman-labelled probe. This sensor system has been applied to detect a specific Anthrax biomarker by means of peptide functionalised GNPs,[339] and detect specific DNA sequences such as HIV DNA using Raman-active dye labelled DNA on GNPs or AgNPs.[340–343] Similarly, detection of hepatitis B virus antigen was reported using GNPs-antibody conjugates with 4-mercaptobenzoic acid (MBA) acting as a Raman-active probe.[344] Also, the detection of viral pathogens using monoclonal antibody conjugated GNPs and a Raman reporter has also been studied.[386] In a separate study, a molecular nano-beacon approach using a Raman dye-labelled DNA functionalised on AgNPs was applied to detect and quantify a gag gene sequence of the HIV-1.[387] Here, the presence of a complementary target decreased the SERS signal as a consequence of the disruption of the hairpin structure that would otherwise place the Raman dye in proximity to the NP's metallic surface. This method has been further expanded successfully to detect the erbB-2 and ki-67 breast cancer biomarkers using gold nanobeacons.[345]

A nanocomposite of PtNPs and graphene oxide has been successfully used as signal transducer to develop a colour-based assay for the detection of cancer cells by deploying folic acid functionalised nanocomposite of PtNPs and graphene oxide. Folic acid acts as a recognition factor since folate receptors are over expressed on the cell membranes of different types of cancer cells.[346] The result obtained above is due to the peroxidase-like activity of the nanocomposite, which catalyses the oxidation of 3,3',5,5'-tetramethylbenzidine (TMB) by H_2O_2. Another example of the peroxidase activity of PtNPs has been applied in enzyme-linked immunosorbent assays (ELISAs), a nanohybrid of magnetic nanoparticles and PtNPs was immobilised on the surface of graphene oxide. This sandwich of nanocomposite was effectively used for the colorimetric detection of cancer cells via reaction of the peroxidase substrate, TMB.[347]

Electrochemical immunoassays (EIs) have been widely reported due to their high sensitivity, simplicity, and low cost. NMN-based electrochemical immunodetection offers added advantages such as high conductivity and large surface-to-volume ratio. These nanoscale materials are promising future candidates as signal tags for the development of electrochemical platforms for immunosensing. The tuneability of noble metal nanoparticles in terms of size, shape, and surface conjugation has yielded positive results in amplification and enhancement of electrochemical immunosensing signals. Development of an accurate and sensitive electrochemical immunosensor requires signal amplification and background noise reduction owing to the relatively weak electrochemical action of the immunocomplex.[388,389] Enzyme labels are generally used for this purpose, but due to the instability issues related to most enzymes, there is interest in nano-templates as alternatives for signal enhancement.[390–392] Preparation of non-enzymatic electrochemical immunoassays (NEEIs) based on nanoscale system can be used for two purposes. First, they can be applied to transform the electrochemical transducer matrix, which will result in low background noise and fast electron transfer, and secondly as tags for the amplification of the signals. NMN seem to be well suited to the development of NEEIs because of their highly stable nature, conductivity, biocompatibility, and catalytic efficiency.[393,394] The large surface area of noble metal nanoparticles together with their ease of surface functionalisation with biomolecules (e.g. antibodies), electroactive tags and polymers, makes them a promising and interesting candidate for these systems. GNPs and PtNPs of various sizes, shapes, and structures are inherently capable of catalysing oxidation, hydrogenation, and dehydrogenation of innumerable analytes,[395] and these properties of noble metal nanosystems can be successfully employed for the development of sensitive, reliable and cost-effective NEEIs. The introduction of GNPs in NEEIs as electrode materials for the immobilisation of biomolecules has produced significant results.[396] GNPs are capable of binding a wide range of substances to build up an efficient electrochemical transducer surface, containing amino acid, protein, porous silica, metal nanoparticles, and carbon nanomaterials.[397–403] In this regard, an effective impedimetric immunoassay was developed based on GNP-modified graphene paper electrode for the rapid and sensitive detection of *E. coli* 0157:H7.[348] A biocompatible nanocomposite comprising of GNPs and 4-amino-1-(-3-mercapto-propyl)-pyridine hexafluorophosphate was developed for sensing human IgG concentration with high sensitivity.[349] Another such nanocomposite containing GNP-graphene oxide and polydopamine-thionine was effectively used for developing a label-free electrochemical immunoassay system for determination of alpha-fetoprotein.[350] The charge transfer and high conductivity properties of GNPs greatly enhanced the sensitivity of this detection method. Palladium nanoparticles (PdNPs) are another important noble metal nanoparticle, which has been utilised as electrode material due to its high catalytic efficiency. Palladium nanoplates, ultrathin metal films, have also been successfully used for amperometric immunoassay for the accurate detection of alpha-fetoprotein.[351] The sensitive detection of these cancer biomarkers was due to excellent electrochemical properties of the nanoplates, which enhanced the electrochemical signal. PdNPs with a reduced graphene oxide-based electrochemical immunodetection system have been fabricated for the development of prostate-specific antigen. Low concentrations of these antigens could be detected using this decorated electrode due to the synergistic electrochemical activities of PdNPs and the reduced graphene oxide.[352]

Signal amplification is key to the development of efficient and highly specific electrochemical immunosensors with low limits of detection (LOD) and high sensitivity. Noble metal nanoparticles have been used for signal amplification in NEEIs utilising 3 different strategies; (i) as electroactive labels, (ii) as carriers, and (iii) as electrocatalytic labels. Direct application of NMN as electroactive tags has shown promising results in signal enhancement. This method comprises two stages. Firstly, strong oxidants are used to dissolve the NMN into their metallic form, and secondly stripping voltammetry is employed for the sensitive detection of the dissolved ions. Utilising this method, a group of researchers synthesised a nanohybrid of AgNPs and titanium phosphate and applied it as a label for electrochemical immunodetection of human interleukin-6.[353] In the presence of the target antigen, the nanohybrid of AgNPs and titanium phosphate was anchored to the magnetically modified sensing array through sandwich-typed immunoreactions and upon addition of a strong oxidant, the Ag^+ ions are released from the complex. This system achieved an excellent LOD for IL-6. In a separate study, AgNPs and graphene oxide nanocomposite was used for electrochemical immunodetection of *E. coli* using solid-state voltammetry.[354] GNPs have been used as carriers in NEEIs for loading of multiple electroactive labels for the preparation of functionalised signal tags in order to enhance the immunoreaction system. The most commonly used electroactive labels are thionine, ferrocene and metal ions. The functionalisation of GNPs with 6-ferrocenyl hexanethiol for the development of a sensitive electrochemical immunosensor provided an efficient signal enhancing label for the determination of prostate specific antigen.[355]

In this era of enhanced environmental concern, catalytic reactions play an important role in the field of environmental and material sciences.[404] Growth of pollution from industry and agricultural has posed a life-threatening challenge to human society, in the form of hazardous pollutants such as heavy metals ions, pesticides, dyes, toxic chemicals, pathogens, and contaminants.[405,406] Various optical sensors have been developed for detecting heavy metal ions which include organic dyes,[407,408] fluorescent polymers,[409] and noble metal nanoparticles (**Fig. 11**).[396,410–412] Among these sensors, noble metal nanoparticles have attracted considerable attention owing to their size, shape, chemical and optical properties, high surface-to-volume ratio, good stability, and excellent biocompatibility.[396,413,414] In this section, we described some of the important sensing functionalities of NMN (**Table 5**).

Table 5 Noble metal nanoparticles as detection probes

Type of noble metal nanoparticles	Application	Property	References

GSH modified GNPs	Pb^{2+} detection	LSPR	[415–417]
MTA modified GNPs	Hg^{2+} detection	LSPR	[418,419]
Protein coated gold nanoclusters	Hg^{2+} and CH_3Hg detection	Fluorescence	[420]
BSA-GNPs nanoclusters	Ag^{+} detection	Fluorescence	[307]
Pepsin-gold nanoclusters	Hg^{2+} and Pb^{2+} sensing	Fluorescence	[421]
BSA-gold nanoclusters	Sensing of H_2O_2 and pesticides (dithizone, fenitrothion and paraoxonethyl)	Fluorescence	[422]
AgNPs	Ni^{2+}, Co^{2+}, Cd^{2+}, Pb^{2+} and As^{3+} detection	LSPR	[423]
AgNPs	Hg^{2+} detection	LSPR	[424,425]
Ag nanoclusters	Hg^{2+} sensing	Fluorescence	[426]
Polymethacrylic acid functionalised Ag nanoclusters	Cu^{2+} detection	Fluorescence	[427]
PtNPs	Hg^{2+} detection	LSPR	[428]

GSH modified GNPs with a core size of 5-8 nm have been used for detecting Pb^{2+} ions in solution by a colorimetric method. GSH-GNPs could immediately aggregate in the presence of Pb^{2+} ions which results in a red shift in their SPR peak.[415,416] This method is size-dependent, with a better sensitivity when the core size of the GNPs is bigger. Such colorimetric assays are popular because they can be easily observed with the naked eye or using a UV-vis spectrometer thus providing simple, cost-effective, sensitive, and selective detection of harmful environmental pollutants such as heavy metal ions. In another study, 11-mercaptoundecyl-trimethylammonium (MTA) conjugated GNPs have been investigated for Hg^{2+} ion sensing.[418] The colour of the GNP solution changes from red to blue in the presence of Hg^{2+} ions, which is again evidenced in the UV-visible spectra with a red shift of the absorption peak. The high affinity between Hg^{2+} ions and GNPs have also been utilised for removal of mercury from water using a GNP-Al_2O_3 nanocomposite.[419] The shape of noble metal nanoparticles proves to be a potent regulator in sensing capabilities of heavy metal ions. For example, decahedral GNPs can detect Pb^{2+} ions at 1000-fold lower LOD than their spherical counterparts.[416] Similarly, AgNPs with different shapes such as nanospheres, nanoplates and nanorods have been applied for constructing colorimetric sensors for Co^{2+} ions. Spherical AgNPs showed the highest sensitivity for Ni^{2+}, Co^{2+}, Cd^{2+}, Pb^{2+}, and As^{3+} ions,[423] whereas Ag nanorods possessed greater selectivity for Co^{2+} ions over other metal ions in the solution. It has been shown that AgNPs provide a lower LOD for Hg^{2+} ions than GNPs because the molar extinction co-efficient of AgNPs is about 100-fold greater.[424] This property has been utilised to make cost-effective assays for Hg^{2+} ion detection using mercury-specific oligonucleotides.[425] In the presence of Hg^{2+} ions, the unfolded nucleotides were linked with Hg^{2+} ions, which resulted in aggregation of AgNPs in solution as reflected calorimetrically. PtNPs can also be used for sensing mercury. PtNPs used for this purpose catalyse the reaction between TMB and H_2O_2, which leads to a blue coloured product. However, in the presence of trace amounts of Hg^{2+} ions, this catalytic activity of PtNPs is inhibited.[428] GNPs functionalised with different organic ligands such as thiolates, amino acids, peptides, and DNA, have been described as sensitive colorimetric detectors for heavy metal ions.[425,429] For example, citrate coated GNPs aggregate in presence of Hg^{2+} ions and lysine, because of the strong bond formation between Hg^{2+}-Au (**Fig. 12**).[430] In another example, peptide functionalised GNPs can be deployed for sensing Co^{2+}, Hg^{2+}, Pb^{2+}, Pd^{2+}, and Pt^{2+} ions, respectively.[417]

Moving on to the next property of NMN, that is fluorescence which confers attractive attributes for sensing heavy metal contaminants due to higher emission.[431,432] A desirable sensor system with strong fluorescence can be developed by fine tuning the size, shape, composition, and surface functionalisation of noble metal nanoclusters. Metal nanoclusters with smaller size (i.e. fewer number of metal atoms) often produce higher fluorescence due to their smaller size and larger surface area and these fluorescent probes can be used for sensing heavy metal ions as environmental pollutants.[433] Protein coated gold nanoclusters as a highly fluorescent probe have been successfully used for the detection of Hg^{2+} ions and CH_3Hg^{+} species with low LOD.[420] Traces of Ag^{+} ions are similarly tested using BSA conjugated gold nanoclusters, where the presence of Ag^{+} ions leads to the formation of Ag-Au alloy nanoclusters which in turn produce an increased fluorescent intensity.[434] Ag nanoclusters also exhibit similar fluorescent probing activity for detecting Hg^{2+} ions due to strong interaction between Ag^{+} and Hg^{2+} ions.[426] Metallophilic interaction between metal cores with a closed-shell electronic configuration can be applied for detecting heavy metals ions. As in the case with Ag and Au nanoclusters, a trace amount of Hg^{2+} ions could be effectively detected using this property, which leads to fluorescence quenching of the nanoclusters.[435] Polymethacrylic acid-functionalised Ag nanoclusters were used to detect Cu^{2+} ions, which quenche the fluorescence of Ag nanoclusters in solution.[427] In a separate study, pepsin-conjugated Au nanoclusters were applied for sensing Pb^{2+} ions via fluorescence enhancement and can also be used for Hg^{2+} ion detection by a fluorescence quenching phenomenon.[421] The sensing capabilities of noble metal nanoparticles is not limited to heavy metal ions; they can also be utilised for H_2O_2 and pesticide sensing as well. For example, BSA stabilised gold nanoclusters can detect H_2O_2 and common pesticides such as dithizone, fenitrothion, and paraoxonethyl, using fluorescence detection.[422] Low levels of pesticides such as endosulfan have been sensed by GNPs as well.[436]

Table 6 Biomedical imaging applications of noble metal nanoparticles via LSPR properties.

Type of noble metal nanoparticles	Applications	References
Gold nanoshells	Imaging of prostate cancer cells	437
Gold nanobeacons	Imaging of sentinel lymph nodes	438
Gold nanoshells	Contrast agents in dark-field microscopy for HER 2, a cancer biomarker	188
Gold nanoshells	Imaging of live HER 2 overexpressing cancer cells	439
Gold nanorods, nanocages and nanoclusters	*In vivo* imaging of cancer cells	440,441
PEG-GNPs	Imaging of tumour cells	442,443
Gold nanoshells	Imaging of tumours in mice model	444
Gold nanoshells	Imaging of vasculature of a rat brain	445

Importance of NMN for imaging purposes: The ability of NMN to absorb and scatter light in the NIR region makes them one of the most potent candidates as contrast agents in biomedical imaging (**Table 6**).[441,446,447] The highly permeable nature of human skin and tissues to NIR radiation has led to the development of minimally invasive deep tissue diagnostic imaging methods with noble metal nanoparticles acting as contrast enhancer vectors. The application of noble metal nanostructures in *in vivo* imaging techniques allows certain advantages over conventional NIR organic dyes, such as avoiding rapid photobleaching, better detection sensitivity, improved stability in biological systems, and better multiplexing capability.[447] NMN with light scattering properties enhance the contrast of imaging systems, such as dark-field or dual-photon luminescence microscopy, and also facilitate combined imaging techniques to produce a synergistic effect over single imaging method.[448,449] Since the LSPR of noble metal nanomaterials is located within the NIR region, they have been applied in different imaging modalities like Photo-Acoustic Imaging (PAI), Photo-Acoustic Tomography (PAT) and dark-field and two photon microscopies. In one study, gold nanorods conjugated with an antibody and simultaneously tuned to the NIR region with PAI have been effectively used to image early-stage prostate cancer cells. Here, the gold nanorods resulted in enhanced contrast images between healthy/non-targeted tissue and cancerous/targeted tissue.[437] Gold nanorods as contrast agents for *in vivo* imaging using a laser based PAI system have also been reported.[444] In a complementary approach, gold nanobeacons (2-4 nm) conjugated with PAI were applied for the detection of sentinel lymph nodes in *ex vivo* tissue specimens.[438] In dark-field microscopy, the NIR scattering properties of gold nanoshells has been exploited as contrast for targeting human epidermal growth factor receptor 2 (HER2), a biomarker for cancer.[188] These gold nanoshells were also used to image live HER2-overexpressing cancer cells using two-photon microscopy.[439] Gold nanoshells, nanorods, nanocages, and nanoclusters have shown considerable promise as contrast agents for *in vivo* cancer imaging due to their significant absorbance and scattering in the NIR region.[440,441] These nanoformulations of gold are also used as contrast agents for Surface-Enhanced Raman Scattering (SERS), Photo-Acoustic Imaging (PAI), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Optical Coherence Tomography (OCT).[442,450–455] The use of ~30 nm PEG coated GNPs for *in vivo* CT was shown to increase image contrast by reducing both the radiation dosage needed and other toxic outcomes associated with using conventional contrast agents.[442] The intense light scattering by gold nanoshells has been used to enhance image contrast in OCT to improve diagnostic imaging of tumours in a mice model as a result of nanoshell accumulation near the tumour site.[444] Similarly, in PAI and PAT, the image of circulating gold nanoshells in the vasculature of a rat brain has been shown to enhance image contrast, allowing for a more detailed description of vasculature structures at greater depths.[445] These applications of gold nanostructures are attractive because they provide higher photostability, quantum yield, detection sensitivity, stability in biological systems, and hydrophilicity than conventional organic dyes. Additionally, the intense scattering property of these gold colloids has played an important role in enhancement of image contrast in dark-field microscopy and dual-photon luminescence microscopy.[456] The application of SERS in conjugation with NMN has also been described for the detection and intracellular molecular imaging of living cells and tissues. In this case, 60 nm GNPs coated with PEG and a tumour targeting antibody were able to detect tumours both *in vitro* and *in vivo* through SERS imaging.[443] Here, GNPs were used to detect tumour biomarkers such as epidermal growth factor receptors on cancer cells and in xenograft tumour models more efficiently than NIR-emitting quantum dots. Specific cancer biomarkers like phospholipase Cg1 (PCg1) were also imaged in live HEK293 cell lines by NMN using SERS microscopy.[457] SERS using GNPs attached to a Raman absorption reporter species has been demonstrated to highlight cellular and molecular structures which provide structural information on the cellular milieu inside live cells.[458,459]

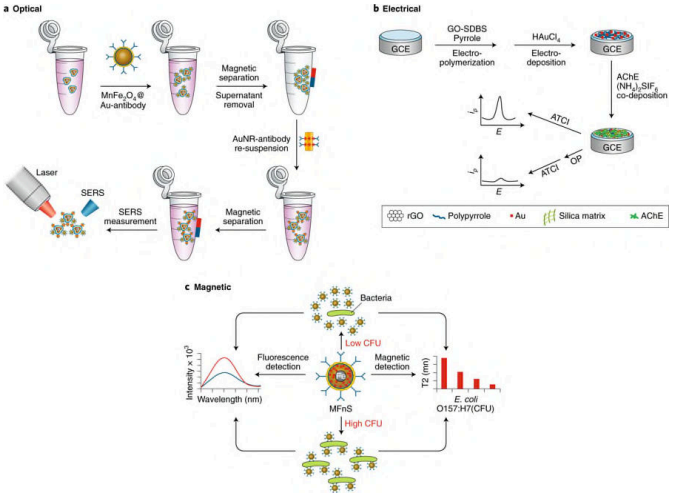


Fig. 11 (a) Surface-Enhanced Raman spectroscopy (SERS)-based detection of magnetically separated bacteria. (b) Preparation and use of a gold/reduced graphene oxide (rGO) nanocomposite-based biosensor and its application for the electrochemical detection of organophosphorus pesticides (OP). (c) Combined magneto-fluorescence approach for detection of bacteria using fluorophore labelled magnetic nanoparticles. Reprinted with permission from ref [460]

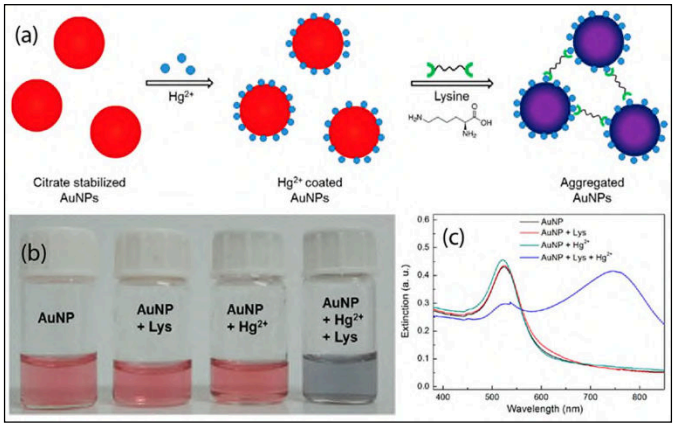


Fig. 12 Schematic representing the Hg^{2+} sensing mechanism of the colorimetric assay, (b) Photographs of AuNP solutions showing that the colour change occurring only in the presence of lysine (0.4 mM) and Hg^{2+} (10 µM) and (c) extinction spectra of the AuNP solutions. Reproduced with permission from ref [430]

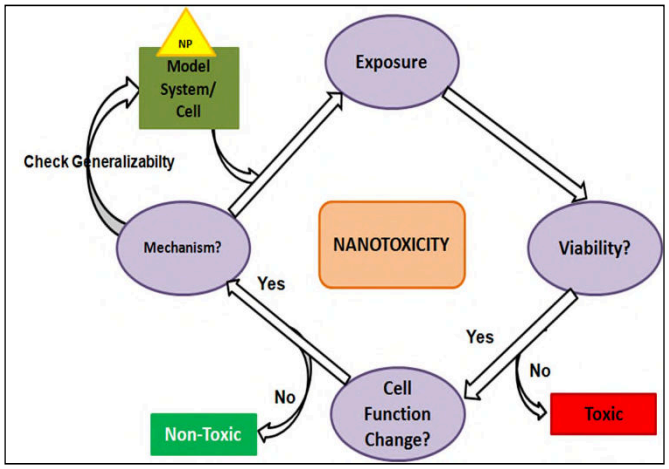


Fig. 13 Schematic representation of toxic effect on animal model system by metallic nanoparticle exposure.

Toxicity Challenge of NMN

The incorporation of noble metal nanostructures in this diverse range of applications has led to increasing concern about their possible toxic impact on human beings and the environment (**Fig. 13**). In general, human beings are exposed to these nanomaterials via inhalation, ingestion, and dermal contact.[461] Reports suggest that NMN tend to exert their toxicity when they either circulate in the bloodstream to organs, tissues and cells, or get absorbed in the spleen or bone marrow (**Table 7**). These absorbed nanomaterials evoke oxidative stress, immune response, cellular apoptosis, and DNA damage upon their entry into the mitochondria and the nuclei.[462] Depending on the size of the nanoparticles, their typical fate after intravenously injection is summarised in **Fig. 14**.[463] Clearance of NMN is a big challenge because these materials are not biodegradable and tend to accumulate in organs such as liver and spleen.[464] The extended persistence of noble metal material can result in unforeseen toxic and adverse effect. The clearance of NPs depends on size, shape, and charges (**Fig. 14**). The two major clearance pathways of NPs are renal and hepatic pathways. The renal pathway is the rapid removal mechanism for clearing vascular compartments and is the desired clearance pathway for NPs.[465] The general size threshold for renal clearance versus hepatic clearance is estimated to be 6 to 8 nm based on the permeability of the glomerular filtration barrier.[465] Therefore one strategy to fabricate safe noble NPs is to make them extremely small.[466,467] However, if the size of NPs becomes too small, they will be cleared from the circulation system prematurely, limiting their ability to carry out the designed action *in vivo*.[468] To overcome this dilemma, researchers have created so-called ultrasmall-in-nano architecture, where ultrasmall noble NPs are assembled into clusters by biodegradable agents.[469,470] These nano-architectures are engineered to degrade over a certain period of time into NPs that are small enough to be excreted via the renal pathway. By using poly(L-lysine) as the assembly agent, Voliani and coworkers fabricated gold ultrasmall-in-nano architectures, which exhibit high photothermal efficiency and are promising for hyperthermia cancer treatment.[470]

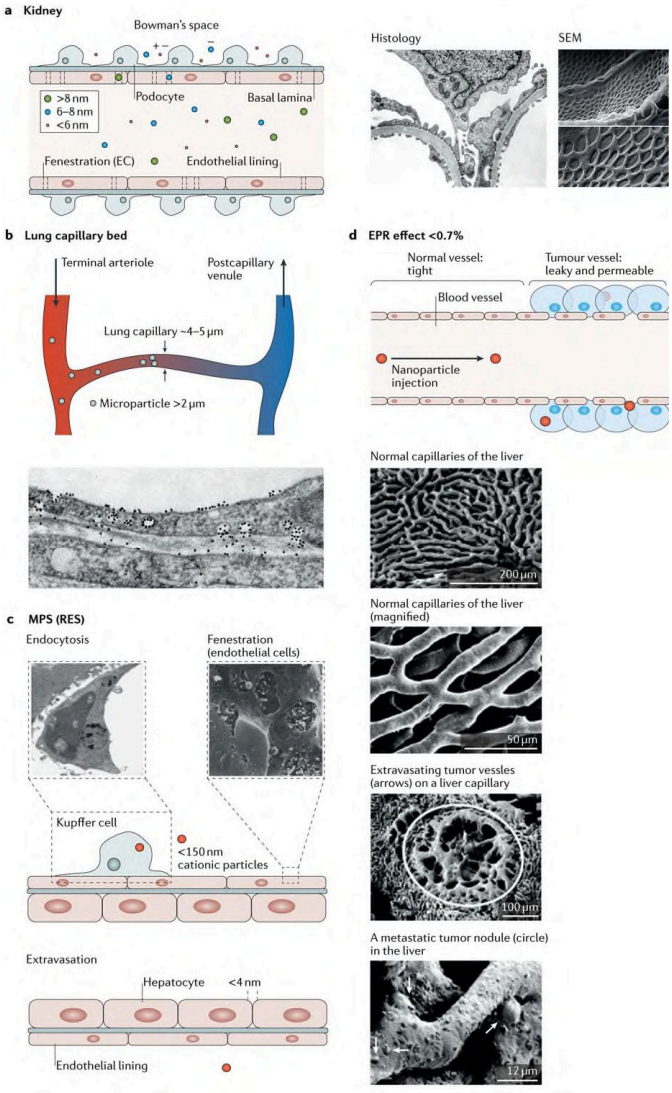


Fig. 14 The fate of nanoparticles and their accumulation and clearance sites. (a) Schematic illustration of kidney filtration or renal clearance of NPs, SEM images and histology of glomerular cell surface (endothelial lining). (b) Schematic illustration lung capillary beds filtration of NPs in the lungs. (c) Schematic illustration of nanoparticle clearance mechanism in liver via endocytosis by Kupffer cells (histology) and fenestration by endothelial cells (SEM); (d) Schematic illustration of the enhanced permeation and

retention (EPR). SEM images of normal and cancerous tissues. MPS, mononuclear phagocytic system; RES, reticuloendothelial system. Reprinted with permission from ref [464]

A size-dependent toxicity study was performed for GNPs on different cell lines such as fibroblast, epithelial cells, macrophages and melanoma cells. The study demonstrated that GNPs in the size range of 1.4-5 nm exhibit toxicity to all the above-mentioned cells, whereas 15 nm GNPs exposure to cells has no profound negative side effects even after 3 days of treatment.[471,472] In a separate study, it was demonstrated that bare GNPs can induced cell-specific killing in a concentration dependent fashion and the accumulation of GNPs is localised in specific cellular domains (**Fig. 15**).[194] Co-incubation of immune cells with citrate capped GNPs (10 nm) showed a little adverse effect on the immunocellular phenotypes and cell death, even after 48 hours of treatment, whereas the cytokine profile (IL-1, IL-6, IL-10 and IL-12) significantly changes which implicates the activation of the immune response upon GNPs treatment.[473]

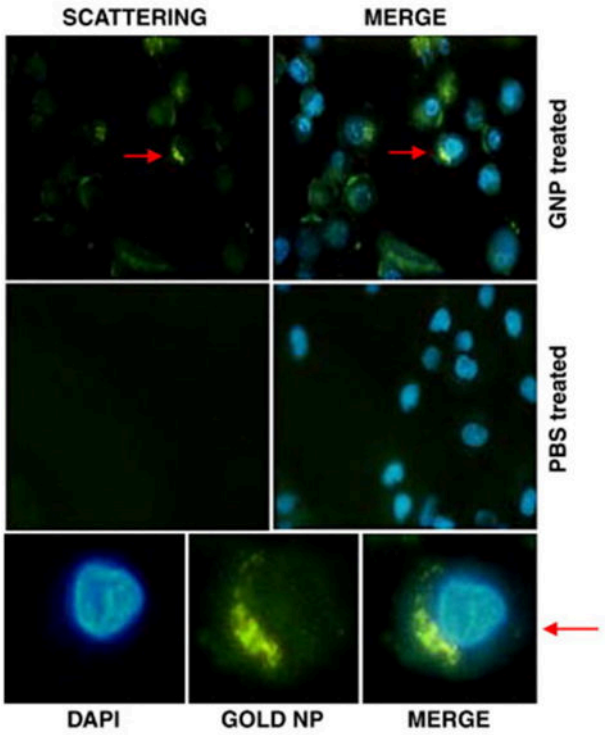


Fig. 15 Intracellular localisation of GNPs in A549 cells. Upper panel: The left column is the scattering of GNPs in the presence and absence of GNPs after excitation in the ultraviolet-visible range (300-450 nm). The right column shows the coexistence of nucleus (DAPI) and GNP scattering, in the presence and absence of GNPs. Lower panel: Magnified version of the red arrow marked cell. Reprinted with permission from ref [194]

It has been reported that 15 nm GNPs coated with triphenyl-phosphine are fairly unreactive in comparison to 1.4 nm GNPs, which cause mitochondrial disruption and generation of free radicals.[474] Similarly, stress related genes were up-regulated upon treatment with 1.4 nm GNPs, but not with 15 nm GNPs, as revealed by gene array analysis.[474] In another study, the epigenetic modulation was observed in lung fibroblasts upon exposure to 20 nm GNPs. Here, GNP treatment caused up-regulation of microRNA-115, down regulation of PROS-1 gene and condensation of chromatin in the nucleus.[475] Gold colloids of 20 nm in size can also trigger oxidative stress autophagy in human lung fibroblasts,[476] which results in elevated lipid peroxidation levels, up-regulation of many autophagy related genes (ATG-7), increase in inflammatory enzyme cyclooxigenase-2 (COX-2), and polynucleotidekinase 3'-phosphate (PNK) gene production.[476] In another example, keratinocytes (HaCaT), when exposed to 1.5 nm GNPs of different charge (positive, negative and neutral), exhibited a noticeable disruption of cellular structure in a dose-dependent manner.[477] The surface charge of GNPs determines the extent of biological response, with charged GNPs promoting apoptosis whereas neutral GNPs lead to necrosis.[478] Similarly, when positively charged GNPs (2 nm) of varying surface hydrophobicity were tested in HeLa cells, the experimental outcome revealed that the higher the hydrophobicity, the greater the observed acute toxicity and production of ROS.[479] It was found that larger surface charge density (effective electric field) of negatively charged GNPs results in higher degree of fluctuation in the cytotoxicity (**Fig. 16**).[480] Recent investigation has revealed that 10 nm GNPs are widely dispersed throughout the body, whereas larger particles were observed only in the liver, blood, and spleen.[481] In a similar study, Wistar-Kyoto rats treated with 10, 20 and 50 nm GNPs for 3-7 days, showed hepatotoxicity and renal toxicity. Smaller sized GNPs had a more deleterious effect than larger particles with concomitant generation of ROS, which led to necrosis, renal tubular modulations, higher Kupffer cell hyperplasia, and central veins intimae disruption.[482] In a separate observation, it was illustrated that GNPs stabilised with non-toxic stabilisers, in this case PEG, also showed size-dependent harmful effects. PEG-GNPs of smaller hydrodynamic diameter (5, 10 and 30 nm) accumulated in the liver and spleen, whereas much larger nanoparticles (60 nm) did not agglomerate in either of these organs.[483] Size and surface charge distribution of GNPs also seem to have a profound negative influence on aquatic life. In a study conducted *in vivo* in a zebra fish model, it was observed that upon exposure to GNPs functionalised with cationic ligands (~1.3 nm), fish embryos exhibited harmful side effects, which included morphological changes such as abnormally small and less pigmented eyes.[484] Depending upon the route of administration, the toxicity profile of NMN varies. For instance, the toxicological features of 13.5 nm GNPs are determined on the route of administration.[485] In this study, mice were injected with GNPs through (i) oral administration, (ii) intraperitoneal administration (IP), and (iii) tail vein injection. Tail vein injection showed minimal toxic effects to white blood cells and platelet counts, on the other hand GNPs administered orally or intraperitoneally exhibited higher level of toxicity with reduction in red blood cell count.[485] The inclusion of AgNPs as an effective and tested antimicrobial agent and in other therapeutic applications has posed an intriguing question regarding their safety profile. The usage of AgNPs for industrial benefits has directly or indirectly presented an enormous threat to human health and environment alike.[486,487] The size, shape, and surface composition of AgNPs are the major contributing factors which affect their intracellular uptake and cytotoxicity.[472] The noxious side effects of AgNPs have been studied thoroughly and in a detailed manner using numerous models like zebra fish,[258] mice, rats,[488] fresh water flea,[489] stem-cells derived fibroblast, and L929 cell line.[490] The deleterious effect of AgNPs leads to harmful ROS generation and lipid peroxidation, which in turn causes DNA damage, necrosis, and apoptosis.[491–493]

In another independent study, it was concluded that AgNPs exert their cytotoxic effect in a size-, shape-, and dose-dependent manner on red blood cells and hepatic stellate cells.[494]

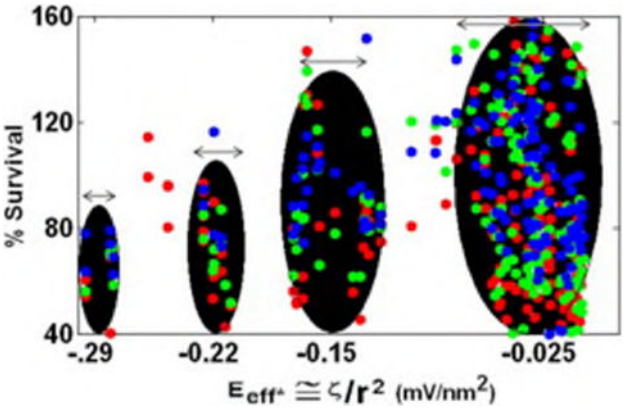


Fig. 16 Cellular survival rate as function of effective electric field for negatively charged GNPs.[480]

A Trojan-horse effect has been suggested in relation to the dose and time-dependent harmful side effects of AgNPs in the RAW246.7 cell line. In this case, after exposure to the nanoparticles, intracellular glutathione (GSH) level decreased, leading to a cascade of reactions which included increased secretion of nitric oxide and increased expression of TNF-α and matrix metalloproteinase,[495] with a complete arrest of the cells at G1 phase of the cell cycle. A cytotoxic study of AgNPs in rat liver cells (BRL 3A) observed that after 24 hours of incubation with AgNPs,[496] there was a significant decrease in the functional attributes of mitochondria and leakage of lactate dehydrogenase (LDH). AgNP toxicity is mediated through oxidative stress, which increases ROS and decreases GSH production.[496] Further investigations clarified the mechanism of cytotoxicity of AgNPs using human Chang liver cells,[497] where it was elucidated that the AgNPs create a loss of mitochondrial membrane potential (MMP) by regulating the expression of the mitochondrial-dependent apoptotic pathway (Bax and Bcl-2).[497] This decrease in MMP results in the release of cytochrome C, which in turn activates caspase-3 and caspase-9. In a more recent and detailed study, it was illustrated that AgNPs contribute to cellular damage.[498] In this experiment, the bioenergetics of rat liver mitochondria was determined upon exposure to AgNPs and it was shown that AgNPs create an increase in the permeability of the inner mitochondrial membrane leading to mitochondrial depolarisation. This functional loss of mitochondrial activity results in an uncoupling effect on the oxidative phosphorylation system.[498] AgNPs, when incubated with liver cells such as human Chang liver and Chinese hamster lung fibroblasts for 24 hours in a dose-dependent study, exhibited overloading of mitochondrial Ca^{2+} ions and greater endoplasmic reticulum (ER) stress.[499] AgNPs can lead to increased phosphorylation of PERK and IRE1 along with an up-regulation of GRP78/Bip, which are ER stress markers, and altogether this induced ER stress upon AgNPs exposure ultimately leading to cellular apoptosis.[499] AgNPs also exhibit cytotoxic effect in coronary endothelial cells (CECs) and aortic rings isolated from rats.[500] In this study, it was observed that AgNPs induce NO-dependent proliferation in a dose and size-dependent manner in CECs.[500] Intravenous administration of AgNPs in Balb/c mice revealed that particles were mostly taken up by the reticuloendothelial system (spleen and liver).[501] However, other reports suggest enhanced liver enzyme activity, higher uptake by local macrophages, increased inflammatory response, and liver damage.[501] The effect of inhalation of AgNPs was performed using Sprague-Dawley rats with 18 nm AgNPs.[502] The rats were exposed to the silver colloids in a whole-body inhalation chamber and the end results indicated that AgNPs reduce lung function and produce inflammatory lesions in the lungs. Oral administration of AgNPs (60 nm) in both male and female rats were extensively studied for a one-month period.[488] This demonstrated that although AgNP treatment did not result in a significant change in body mass index, blood chemistry analysis revealed elevated liver damage as indicated by changes in alkaline phosphatase (ALP) and cholesterol in both groups.[488]

Size-dependent studies on the toxic effects of AgNPs (22, 42, 71,323 nm) by oral administration in mice showed increased toxicity with higher immune cell infiltration (B cell and higher CD8+ T cell) and increased level of TGF-β and cytokine production (IL-10 and IL-12) in 22 nm AgNPs treated mice, whereas larger particles did not produce any alarming side effects.[487] In another study, 20, 80 and 110 nm AgNPs were administered through tail veins and it was concluded that larger nanoparticles mostly accumulate in spleen followed by liver and lung, while 20 nm AgNPs mainly get deposited in the liver and then the kidney and spleen.[503] Concentration dependent dermal toxicity of AgNPs conducted on male guinea pigs showed that at low dose, AgNP-treated animals exhibited a reduction in the thickness of the epidermis and dermis with an increase of inflammatory Langerhans cells.[504] However, when given at higher dose, skin toxicity was apparently observed as a result of disrupted collagen fibres as well as higher macrophage infiltration with acidophilic cytoplasm.[504]

There are relatively fewer reports regarding the toxicity of PtNPs. One report studied the cytotoxic effects of 3 different noble metal nanoparticles (GNPs, AgNPs and PtNPs) using a zebra fish model. It was confirmed that PtNPs induce an increase in the hatching time, a drop-in heart rate, and a reduced touch response in this model.[505] Another study conducted on mice reports that PtNPs cause acute hepatic injury as evidenced by an increased level of serum biomarkers of liver injury and inflammatory cytokines.[506,507] Cytotoxic effect of PtNPs on skin suggest that nanoparticles of larger size and coated with an uncharged non-toxic stabiliser such as PVP have no significant toxic effect, while on the contrary, much smaller sized PtNPs showed deleterious side effects on primary keratinocytes leading to decreased cell metabolism.[508] The presence of these nanomaterials in our day-to-day life is becoming inevitable and therefore a more detailed and thorough investigation needs to be conducted concerning the long-term usage of these engineered nanoparticles for the betterment of human life and society.

Table 7 Toxicity of noble metal nanoparticles.

Type of noble metal nanoparticles	Toxicity	References

GNPs (1.4-5 nm)	Changes in cytokine profile (IL-1, IL-6, IL-10, IL-12)	471–473
GNPs (1.4 nm)	Mitochondrial disruption and generation of free radicals	474
GNPs (1.4 nm)	Up-regulation of stress related genes	474
GNPs (20 nm)	Epigenetic modulation, up-regulation of microRNA-115, down regulation of PROS-1 gene and condensation of chromatin in the nucleus	475
GNPs (20 nm)	Triggers oxidative stress autophagy in lung fibroblasts, increase in lipid peroxidation levels, up-regulation of many autophagy related gene, increase in COX-2 and PNK gene production	476
GNPs (1.5 nm)	Disruption of cellular structure	477
GNPs (1.5 nm, charged and neutral)	Charged GNPs leads to apoptosis while uncharged GNPs leads to necrosis	478
GNPs (2 nm)	Production of ROS, renal tubular modulations	479,482
GNPs (>10 nm)	Deposited in liver, blood and spleen and showed hepatotoxicity and renal toxicity	481,482
PEG-GNPs (5-30 nm)	Accumulates in the liver and spleen	483
AgNPs	ROS generation, lipid peroxidation, DNA damage, necrosis, apoptosis, decrease in intracellular GSH levels, increased nitric oxide secretion, increased TNF-α and increased expression of matrix metalloproteinase	491–495
AgNPs	Loss of functional attributes of mitochondria and leakage of LDH	496
AgNPs	Loss of MMP, regulation of expression of mitochondrial dependent apoptotic pathways	497,498
AgNPs	Overloading of mitochondrial Ca^{2+} and up-regulation of ER stress biomarkers	499
AgNPs	Accumulates in liver and spleen, enhanced liver enzyme activity, higher uptake of local macrophages, increased inflammatory response and liver damage	501
AgNPs	Reduction in liver function and production of inflammatory lesions in the lungs	502
AgNPs	Liver damage	488
AgNPs (22 nm)	Higher immune cell infiltration and increased levels of TGF-β and cytokine production	487
AgNPs	Collagen fibres disruption and increase of inflammatory Langerhans cells	504
PtNPs	Increases hatching time period, drop in heart rate in zebra fish model	505
PtNPs	Acute hepatic injury in liver, increased level of serum biomarkers of liver injury and inflammatory cytokines	506,507
PtNPs	Decrease of cellular metabolism	508

Control Perspectives for the Use of NMN in Biomedical Field

Nanobiotechnology faces a major challenge due to the uncontrolled and unethical use of NMN in a wide array of applications, which can lead to serious and deleterious toxicity to humans and environment. The unparalleled advantages presented by NMN would be of no use unless the burden related to their toxicity is addressed and resolved wisely. In order to nullify or minimise the side effects of NMN, various strategies are being employed by researchers worldwide, such as capping the nanomaterials with suitable compounds which aid in reducing the toxicity, preventing aggregation of noble metal nanoparticles, and last but not least, engineering the size, geometry, and biocompatibility of the nanoparticles for their successful applications in biotechnology.

Capping agents of nanomaterials contribute significantly in the activity profile of NMN. It has been reported that several attributes of capping agents increase the toxicity levels of NMN, hence in order to synthesise biocompatible nanoparticles, it is of primary importance that the capping agents are chosen wisely. In this regard, the use of non-toxic polyvinyl pyrrolidone (PVP) or polyvinyl alcohol (PVA) as a colloid stabiliser has been suggested by various research groups. PVP and gum Arabic (GA) coated AgNPs have shown promising result in reducing the toxic side effects of AgNPs.[509] The wide acceptance of AgNPs as an antimicrobial agent has led to an enormous amount of AgNPs being released in the sewage water bodies, which results in the loss of flora and fauna. This harmful effect of AgNPs can be addressed by using sulphate anions in the sewage water thereby preventing or reducing the highly toxic effect of AgNPs.[510] The functional attributes of NMN are directly positively proportional to their surface area. In the case of agglomeration or aggregation of NMN, reduction in surface area occurs and this is ultimately reflected in activity loss. Hence, the problem of particle aggregation should be one of the main focus for nanotechnologists. In one study, it has been shown that bovine serum albumin (BSA) provides a better colloidal stability to GNPs as a capping agent than does citrate anions. This is because the electrostatic repulsion offered by citrate anion can be compromised by Na^+ ions from the saline solution, which leads to aggregation of GNPs, while BSA adsorbed on to the surface of the GNPs helps to prevent agglomeration even under harsh conditions.[511] In another study, the aggregation behaviour of platinum colloids was studied in solution using tetradecyltrimethylammonium bromide (C_{14}TAB), cetyltrimethylammonium bromide (C_{16}TAB) and nonylphenolethoxylate (NP9). TEM analysis revealed that the aggregation of PtNPs reduced considerably when CTAB and NP9 were used as surfactants.[512] In addition to polyethylene glycol (PEG), PVP, natural polymers such as dextran, chitosan, pullulan, and surfactants like sodium oleate and dodecylamine have also shown promising results in preventing aggregation of NMN.[513] Another important aspect of nanotechnology lies in controlling the size of the nanoparticles and maintaining reproducibility, since the chemical properties of bulk noble metals are different in comparison to their nanoscale version. Citrate ions represent one of the most widely accepted reductants for the synthesis of metallic nanomaterials. Size-controlled synthesis of AgNPs was successfully achieved using citrate ions owing to the slow crystal growth as a result of interaction between silver and citrate ions.[514] In a separate experiment, size-controlled preparation of AgNPs was performed using silver and glucose under autoclaved condition. By regulating the concentration of glucose, the researchers were able to produce AgNPs of small, medium, and large sizes in a controlled and reproducible manner. Also, the caramel formed during the autoclaving of glucose functions as the stabilising agent for AgNPs, which in turn reduces their toxicity and increases the biocompatibility of the AgNPs.[515] In a similar manner, size-controlled synthesis of GNPs was also conducted by UV irradiation at room temperature in the presence of air (5-20 nm). In this study, medium sized and larger GNPs (25-110 nm) were also successfully obtained by using ascorbic acid as a reductant.[516] Therefore, by utilising the above-mentioned strategies for noble metal nanoparticles, the toxicity indices of these particles can be checked, which will help to expand their usefulness for biotechnological applications.

Future prospects

In this review, we have endeavoured to illustrate the ever growing and increasingly broad applications of noble metal nanomaterials in the therapeutics, diagnostics, and biosensing fields. Nanostructures have yielded significant positive results towards the betterment of human health, which is being reflected in their wide range of applications in the health sector.

Metallic nanoparticles have found significant utility over a diverse spectrum of biomedical activities such as imaging, sensing, and therapeutics. They have provided an invaluable advance in the detection, diagnosis, and therapy of different human cancers and this has led to the development of a completely new discipline, nano-oncology. Colloids of gold, silver, platinum, and palladium have been widely used and accepted in clinical trials for treatment of cancer. Nanostructures have attracted considerable interest as theranostic agents, but their pharmacokinetics, biodistribution, side effects, and safety profile within the human body, need more thorough investigation for future applications.[360,517–519] The antibacterial, antifungal, antiviral, and antimicrobial properties of plasmonic nanomaterials are already well established and this could be a future strategic approach for the design and development of nanodrugs in the pharmaceutical industries. Toxicological studies based on numerous nanocomposites have provided sufficient data regarding their non-toxicity, but possible toxic side effects upon incorporation into the human body cannot be ruled out completely. The biocompatibility issue related to nanomaterials can be addressed by considering: (i) the dose of nanoparticles used and (ii) the surface modulation. These two aspects in conjunction provide a reliable and sufficient approach to the use of nanomaterials in clinical applications. It is of utmost importance to test nanoparticles and biological interactions in order to modify the nanostructures for optimal biocompatibility and thereby prevent damage to healthy tissues. There are other lesser known NMN such as Rh, Ru, Ir, and

Os nanocomposites, whose diagnostic, sensing, and therapeutic abilities need to be understood in more detail and there is still much work to be done in the area to realise the full benefits of nanobiotechnology in the field of healthcare and environmental preservation.

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