WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 7, 553-563. Review Article ISSN 2277– 7105

# BIOLOGICAL APPLICATIONS OF METAL NANOPARTICLES: A REVIEW

**Sharmistha Banerjee*, Rajesh Singh Tomar and Shuchi Kaushik**

Amity University Madhya Pradesh, Gwalior, Madhya Pradesh-474005, INDIA.

Article Received on
25 April 2015,

Revised on 16 May 2015,
Accepted on 06 June 2015.

***Correspondence for Author**
**Sharmistha Banerjee**
Amity University Madhya Pradesh, Gwalior, Madhya Pradesh-474005, INDIA.

## ABSTRACT

Nanotechnology has prompted new and improved materials for biomedical applications with particular emphasis in therapy and diagnostics. Special interest has been directed at providing enhanced molecular therapeutics for cancer, where conventional approaches do not effectively differentiate between cancerous and normal cells; that is, they lack specificity. This normally causes systemic toxicity and severe and adverse side effects with concomitant loss of quality of life. Because of their small size, nanoparticles can readily interact with biomolecules both at surface and inside cells, yielding better signals and target specificity for diagnostics and therapeutics. Noble metal nanoparticles show unique physicochemical properties (such as ease of functionalization via simple chemistry and high surface-to-volume ratios) that allied with their unique spectral and optical properties have prompted the development of a plethora of biosensing platforms. Additionally, they also provide an additional or enhanced layer of application for commonly used techniques, such as fluorescence, infrared and Raman spectroscopy. Herein we review the use of noble metal nanoparticles for labeling, delivering, sensing, imaging and as anti bacterial agents.

**KEYWORDS:** Biomedical, Diagonostic, Labelling, Functionalization, Imaging.

## INTRODUCTION

Nanoparticles (NPs), and noble metal NPs in particular, are versatile agents with a variety of biomedical applications including their use in highly sensitive diagnostic assays,[1,2] thermal ablation, and radiotherapy enhancement,[3,4,5] as well as drug and gene delivery.[7,8,9,10] Moreover, noble metal NPs have been proposed as nontoxic carriers for drug and gene-delivery applications.[11,12,13] Additionally, the nanoparticle-based systems can provide

simultaneous diagnostic and therapy, that is, Theranostics, exploring their unique properties for better penetration of therapeutic moieties and tracking within the body, allowing a more efficient therapy with a reduced risk in comparison to conventional therapies.[14]

The unique characteristics of noble metal NPs, such as high surface-to-volume ratio, broad optical properties, ease of synthesis, and facile surface chemistry and functionalization hold pledge in the clinical field for cancer therapeutics.[11,15,16] Noble metal NPs (e.g., gold, silver, or a combination of both) present highly tunable optical properties, which can be easily tuned to desirable wavelengths according to their shape (e.g., nanoparticles, nanoshells, nanorods, etc.), size (e.g., 1 to 100 nm), and composition (e.g., core/shell or alloy noble metals), enabling their imaging and photothermal applications under native tissue.[17,18] These NPs can also be easily functionalized with various moieties, such as antibodies, peptides, and/or DNA/RNA to specifically target different cells,[19] and with biocompatible polymers (e.g., polyethylene glycol and PEG) to prolong their *in vivo* circulation for drug and gene delivery applications. [12, 13] Moreover, they can efficiently convert light or radiofrequencies into heat, thus enabling thermal ablation of targeted cancer cells.[20, 21]

The application of metal nanoparticles in biological science showed very rapid progress in the area of labelling, delivery, sensing, imaging and antibacterial agents.

**1. Labelling**

For labelling, electron absorbing properties of the metal nanoparticles are exploited to generate contrast. Gold Nanoparticles (AuNPs) strongly absorb electrons, which make them suitable to be used as a contrast agent in Transmission Electron Microscope. Besides, nanoparticles have the same size domain as proteins that make nanomaterials suitable for bio tagging or labeling.[16] Due to their small size and functionalizing properties, i.e. with antibodies (immunostaining), AuNPs provide extremely high spatial resolution and hence applied in many labelling applications. Additionally optical detection techniques are wide spread in biological research because of change of their optical or fluorescence properties.

Similarly, the particle's optical properties- strong absorption, scattering and especially plasmon resonance- make them of value for a large variety of light-based techniques including combined schemes such as photothermal or photo-acoustic imaging. In addition, AuNPs can be radioactively-labelled by neutron activation, which allows for very sensitive detection, and used as an x-ray contrast agent.[22]

## 2. Sensors

Metal nanoparticles can also be used as sensors. Numerous studies on the labelling of bioassays and the staining of biological tissues by metal particles as a means to image and visualize biological processes have been reported. The spectral shifts which originate from adjacent or aggregated metal nanoparticles, such as Au NPs, are of increasing interest in the development of optical biosensors based on biomolecule–nanoparticle hybrid systems. As an example, nanoparticles that were functionalized with two kinds of nucleic acid, which were complementary to two segments of an analyzed DNA, were hybridized with the analyzed DNA. This led to the aggregation of the NPs and to the detection of a red shifted inter particle plasmon absorbance of the nanoparticle aggregate.[22]

## 3. Drug Delivery

Delivering the drugs precisely and safely to their target sites at the right time to have a controlled release and achieve the maximum therapeutic effect is a key issue in the design and development of novel drug delivery systems. Because of their small size, nanoparticle drug carriers can bypass the blood-brain barrier and the tight epithelial junctions of the skin that normally impede delivery of drugs to the desired target site. Secondly, as a result of their high surface area to volume ratio, nanocarriers show improved pharmacokinetics and bio distribution of therapeutic agents and thus minimize toxicity by their preferential accumulation at the target site. They improve the solubility of hydrophobic compounds and render them suitable for parenteral administration. Furthermore, they increase the stability of a variety of therapeutic agents like peptides and oligonucleotides. Magnetic nanoparticles like $Fe_3O_4$ (magnetite) and $Fe_2O_3$ (maghemite) are known to be biocompatible. They have been actively investigated for targeted cancer treatment (magnetic hyperthermia), stem cell sorting and manipulation, guided drug delivery, gene therapy and DNA analysis, and Magnetic Resonance Imaging (MRI). In another study, Sun *et al*. in 2007[23] loaded doxorubicin (DOX) onto bacterial magnetosomes (BMs) through covalent attachment and evaluated the ability of these particles to inhibit tumor growth. Magnetotactic bacteria (MTB) MC-1 with magnetosomes were also used as drug delivery agent. [24]

Because of nontoxicity and nonimmunogenicity, AuNPs are ideal for preparation of drug delivery scaffold. Functionalization property of AuNPs also makes them an excellent potential vehicle for the drug delivery. Functionalized AuNPs represent highly attractive and promising candidate in the applications of drug delivery. The surfaces of AuNPs can also be

readily modified with ligands containing functional groups such as thiols, phosphines, and amines, which exhibit affinity for gold surfaces. AuNPs have emerged as a promising scaffold for drug and gene delivery that provide a useful complement to more traditional delivery vehicles.[24]

AuNPs and infrared light based drug delivery system was developed. This delivery system released multiple drugs in a controlled fashion. They demonstrated that nanoparticles of different shapes respond to different infrared wavelengths. For example, nanobones and nanocapsules melt at light wavelengths of 1,100 and 800 nm, respectively. Thus excitation at one wavelength could selectively melt one type of gold nanorods and selectively release one type of DNA strand.[22]

Brown *et al*. in 2010 [25] also used AuNPs for the improved anticancer drug delivery of the active component of oxaliplatin. The cytotoxicity, drug uptake, and localization in the A549 lung epithelial cancer cell line and the colon cancer cell lines HCT116, HCT15, HT29, and RKO were examined for platinum-tethered nanoparticles.[22]

It is anticipated that nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage of anticancer drugs with better specificity, enhanced efficacy, and low toxicities. Due to cancer heterogeneity and development of drug resistance, any particular targeted therapy may not be effective for every population of patients. Moreover, magnetic nanoparticles can be used for hyperthermia cancer treatment. Hyperthermia cancer treatment involves administering magnetic nanoparticles into the body, specifically at cancer tissue sites. Local heating at specific sites is enabled by means of an external magnetic field.[24]

## 4. Cancer Therapy

Nanoparticles also carry the potential for targeted and time-release drugs. A potent dose of drugs could be delivered to a specific area but engineered to release over a planned period to ensure maximum effectiveness and the patient's safety. The strong light absorbing properties of AuNPs makes it suitable as heat mediating objects; the absorbed light energy is dissipated into the surrounding of the particles, generating an elevated temperature in their vicinity. This effect can be used to open polymer microcapsules, for example, for drug delivery purposes and even destroys the cancerous cells. The nanoparticles are functionalised with antibody specific to the cancerous cells. The functionalized nanoparticles specifically bind with the targeting cells, which was then killed by hyperthermal therapy through heating the particle-

loaded tissue. However, for such in vivo applications, the potential cytotoxicity of the nanoparticles might become an issue and should be investigated with care. Due to biocompatibility and hyperthermal activity, AuNPs find wide application now a days in killing of malignant cancerous cells.[26] Melancon *et al*.[27] in 2008 demonstrated destruction of cancerous cell by photothermal effect of AuNPs. The hollow gold nanoshells (HAuNS; average diameter, 30 nm) were covalently attached to monoclonal antibody directed to the epidermal growth factor receptor (EGFR). The resulting anti-EGFR-HAuNS exhibited excellent colloidal stability and efficient photothermal effect in the near-infrared region. Anti-EGFR-HAuNS then bound in EGFR-positive A431 tumor cells. Irradiation of A431 cells treated with anti-EGFR-HAuNS with near-infrared laser resulted in selective destruction of these cells.

AuNPs has also been applied to amplify the biorecognition of the anticancer drug.[28] Dacarbazine [5-(3, 3-dimethy-1-triazenyl) imidazole-4-carboxamide; DTIC] is a commonly used anticancer drug. AuNPs were stabilized by PPh3 (Tri phenyl phosphine) with negative charge. The oxidized DTIC is positive charged. Thus, DTIC could be easily assembled onto the surface of AuNPs. The specific interactions between anticancer drug DTIC and DNA or DNA bases were facilitated by AuNPs.[22]

## 5. Environmental Cleanup

Although Metallic Nanoparticles (MNPs) are increasingly being employed in different emergent areas, their use in environmental biotechnology is still limited. One of the key environmental challenges is the contamination of water bodies by different chemicals due to diverse anthropogenic and industrial activities. The most interesting application of MNPs is purification of drinking water contaminated with heavy metals and pesticides. Current limitations in removal of heavy metals have been tried to overcome through adsorption process on MNPs due to alloy formation. Gold and mercury exist in several phases such as $Au_3Hg$, AuHg, and $AuHg_3$.

Recently colorimetric detections of heavy metals like arsenic, mercury, lead, etc., have also been tried by using MNPs. One of the important properties exhibited by functionalized MNPs surfaces is the detection of heavy metals. In one such method, heavy metal specific biomolecule functionalized AuNP can be utilized. An example of this approach is the interaction of metal ions with nucleotides: $Hg^{+2}$ promoted formation of thymine–thymine base pairs. [29] In a similar approach, ligands functionalized MNPs have been used for specific

detection of metal ions. This ligand-metal ion complexation leads to observable optical changes at concentrations in the ppm level. Examples of such ligands are gallic acid ($Pb^{+2}$), cysteine ($Hg^{+2}$, $Cu^{+2}$), and mercapto undecanoic acid ($Pb^{+2}$, $Cd^{+2}$, $Hg^{+2}$). The removal of pesticides by MNPs is a new addition to this field. Among other contaminants, presence of pesticide residue in potable water above permissible limit is of great concern to public health. It is essential to reduce the concentration of pesticide in potable water but difficult to achieve by conventional chemical methods due to wide variation of their chemical structures. To meet these environmental challenges, very recently researchers are focusing on the development of methods based on nanotechnology. Very recently, Das *et al* (2009)[30] demonstrated adsorption of different organophosphorous pesticides on the surface of AuNPs. AuNPs was synthesized on the surface of the *R. oryzae* mycelia in a single set. The AuNPs adsorbed on mycelia were then used for adsorption of different organophosphorous pesticides.[22]

## 6. Antibacterial agent

With the prevalence and increase of microorganisms resistant to multiple antibiotics, silver based antiseptics have been emphasized in recent years. Silver nanoparticles were biosynthesized using fungus *Trichoderma viride* [31] It was observed that the aqueous silver ($Ag^{+}$) ions, when exposed to a filtrate of *T. viride*, were reduced in solution, thereby leading to the formation of extremely stable silver nanoparticles with the size of 5–40 nm. The nanoparticles were also evaluated for their increased antimicrobial activities with various antibiotics against Gram-positive and Gram-negative bacteria. Dur´an and coworkers in 2007 [32] showed that extracellularly produced silver nanoparticles using *Fusarium oxysporum* can be incorporated into textile fabrics to prevent or minimize infection with pathogenic bacteria such as *Staphylococcus aureus*.

## Imaging

Along with their therapeutic capabilities, most noble metal NPs can be used for the simultaneous actuation and tracking *in vivo*. Because light absorption from biologic tissue components is minimized at near infrared (NIR) wavelengths, most noble metal NPs for *in vivo* imaging and therapy have been designed to strongly absorb in the NIR so as to be used as effective contrast agents. However, noble metal nanomaterials, such as NPs, nanoshells, nanoclusters, nanocages, and nanorods, have showed widespread application as contrast agents for *in vivo* cancer imaging: those presenting a significant absorbance and scattering in the NIR region or Surface-Enhanced Raman Scattering (SERS), or as contrast agents for

Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Optical Coherence Tomography (OCT), and Photoacoustic Imaging (PAI).[33]

Hybrid nanoparticles with a super-paramagnetic iron oxide/silica core and a gold nanoshell, with significant absorbance and scattering in the NIR (Near Infra Red) region, have been used *in vivo* as dual contrast agents for CT and MRI presenting high CT attenuation and a good MR signal in hepatoma, compensating for the weakness of each modality.[34]

Tseng *et al*.[35] in 2010, developed nano rings with a localized surface plasmon resonance covering a spectral range of 1300 nm that produced both photothermal and image contrast enhancement effects in OCT when delivered into pig adipose samples. Similarly, gold capped nano roses have been used in photothermal OCT to detect macrophages in *ex vivo* rabbit arteries.[36]

Photoacoustic imaging (PAI) and Photoacoustic Tomography (PAT) are non invasive imaging techniques capable of resolving the optical absorption map of tissue at penetration depths akin with ultrasound imaging. In 2004, Wang and coworkers [37] have used PAT technique to image the distribution of Au nanoshells circulating in the vasculature of a rat brain by achieving a gradual enhancement of the NIR optical absorption in the brain vessels.

Song *et al*. in 2010[38] proposed a noninvasive *in vivo* spectroscopic photoacoustic sentinel lymph node mapping using gold nanorods as lymph node tracers in a rat model. Also, noble metal NP probes can be used for *in situ* diagnostics of cancer. For example, nanoparticle-based NIR probes can overcome several limitations of conventional NIR organic dyes, such as poor hydrophilicity and photostability, low quantum yield and detection sensitivity, insufficient stability in biological systems, and weak multiplexing capability. Additionally, the high scattering properties of these nanoparticles can enhance contrast of imaging systems based on microscopy, such as dark-field or dual-photon luminescence microscopy.

Zhang *et al*. in 2010,[39] developed fluorescent metal nanoshells as molecular imaging agents to detect single microRNA (miRNA) molecules in lung cancer cells. These metal nanoshells were composed of silica spheres with encapsulated $Ru(bpy)_3^{2+}$ complexes as core and thin silver layers as shell. Loo *et al*. in 2005, [40] demonstrated the use of NIR scattering Au-nano shells as a contrast agent in dark-field microscopy to target anti human epidermal growth factor receptor 2 (HER2), a clinically significant breast cancer molecular marker. These Au

nano shells were also used by Bickford *et al*. in 2008[41] for imaging live HER2-overexpressing cancer cells using two-photon microscopy.

## CONCLUSIONS

Nanotechnology has provided for novel and powerful systems that may be used treatment and diagnostic of cancer. *In vivo* demonstrations of noble metal NPs as theranostic agents are now emerging and serve as important milestones towards clinical application. Nonetheless, the majority of products, reagents and drugs being used for the development of these nano scale theranostic agents have still to be approved by the main supervising agencies, such as the FDA and EMA. Thus far, there are some questions whose answers still provide no clear understanding about the design and application of NPs, such as pharmacokinetics, biodistribution and side effects of the nano therapy, and safety profile of NPs before and after conjugation and toxicity. Even though there is no general mechanism for making NPs universally "nontoxic" to all living cells and all organisms, there are important findings that can be applied for increasing nanoparticles biocompatibility and reducing cytotoxic interactions *in vivo* and *in vitro*. In general, using the lowest NP dose to get the desired response for the shortest period of time seems to promote biocompatibility. The coating/capping of a nanoparticle is also of the utmost relevance, since a noncontinuous covering, the presence of cracks, roughness, or interruptions could lead to complement or antibody attachment, or dissolution of the coating by cell digestion, decreasing bioavailability at target cell. Noble metal nanoparticles have shown to be powerful tools against cancer though still in need of further optimization and characterization for full understanding of their whole potential.

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