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Gold Nanoparticles for Applications in Drug Delivery Systems

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Abstract—*During the last decade, nanotechnology has emerged as a vital alternative for the therapy of human diseases. Novel nanomaterials have been developed with applications in the therapy of various human diseases. Common nanomaterials applicable in biomedical applications include quantum dots, liposomes, ferroferric oxide nanoparticles, polymeric micelles, graphene, gold nanoparticles (Au NPs), carbon nanotubes and so on. Among these, gold nanoparticles due to its unique chemical and physical properties have been considered as an important nanomaterial for therapeutic applications. The scientific world has pinned great hope on these nanomaterials as support for the treatment of various diseases. This paper will focus on latest advances in the field of Au NPs as drug delivery systems for the intracellular delivery of therapeutics.*

Keywords*: Gold nanoparticles; Drug delivery; Cancer cells; Gold nanoparticle drug conjugate.*

1. INTRODUCTION

Nanotechnology has attracted a great interest in recent years due to its expected impact on many areas such as energy, medicine, electronics, and space industries. Research in this field has been growing dramatically throughout the world over the last decade. The development of new materials with nanometer size, including nanoparticles, nanotubes, nanowires, etc., is the major activity. Among all, nanoparticles with the unique properties in chemistry, optics, electronics, and magnetics have led to an increasing interest in their synthesis. Nanoparticles are usually referred to as particles in the range of 1–100 nm. Nanoparticles exhibit completely new or improved properties compared to larger particles of the bulk material and these novel properties are derived due to the variation in specific characteristics such as size, distribution and morphology of the particles. The nanoparticles of profound interest are gold, silver, zinc and titanium. Gold nanoparticles, in particular, are of interest, mainly due to their stability under atmospheric conditions, resistance to oxidation and biocompatibility. Today the development of nano-devices using biological materials and their use in wide array of applications on living organisms has recently attracted the attention of biologists towards nanobiotechnology [1].

Nanoparticles have been synthesized by various physical and chemical processes; however, some chemical methods cannot avoid the use of toxic chemicals in the synthesis process. Recently, there has been tremendous excitement in the study of nanoparticles synthesis by using some natural biological system. The use of microbial cells for the synthesis of nanosized materials has recently emerged as a novel approach for the synthesis of metal nanoparticles. Many microbes are known to produce inorganic nanostructures and metallic nanoparticles with properties similar to chemically-synthesized materials, while exercising strict control over size, shape and composition of the particles. Examples include the formation of magnetic nanoparticles by magnetotactic bacteria, the production of silver nanoparticles by *Pseudomonas stutzeri*, synthesis of nano-scale, semi-conducting CdS crystals in the yeast *Schizosaccharomyces pombe* and the formation of palladium nanoparticles using sulphate reducing bacteria in the presence of an exogenous electron donor. Heterotrophic sulfate-reducing bacteria can form ZnS particles with a diameter of 2–5 nm. *Lactobacillus* sp. can synthesis spherical aggregates of TiO2 nanoparticles. These titanium nanoparticles were lighter in weight and high resistance to corrosion.

The ability of bacteria, fungi, actinomycetes, yeast, algae and plants to accumulate gold ions from solution has been reported and the synthesis of gold nanoparticles has been successfully demonstrated in a range of organisms including *Bacillus* sp, fungal species such as *Verticillium* and *Fusarium*, actinomycete such as *Rhodococcus* and *Thermomonospora* and lactic acid bacteria [2].

The nanoparticles have a wide range of applications including food industry, combating microbes, drug delivery, textile industry, catalysis, water purification, treatment of environmental waste, biolabelling and in the treatment of cancer. Nanotechnology is crucial for finding potential applications of nanoparticles for efficient drug delivery [3].

Drug delivery system (DDS) is a fascinating field for the researchers as the delivery of drug is as important as the drug itself. It is a process for the release of the bounded active drug

at a certain speed and at a specific location. Ideally, DDS is cheap, non-toxic and straightforward to make, as well as stable prior to its administration. It is very important to improve specific drug-delivery methods to turn them into clinical realities. Most drugs are limited by their pharmacodynamics properties as well as cytotoxicity and aggregation due to poor solubility, nonspecific delivery, in vivo short circulating half-lives. Physiology poses key challenges to effective drug delivery; an administered drug must penetrate obstacles such as endo- or epithelial membranes and also survive the host's defenses in order to be effective [4].

Nanomaterials offer enormous probabilities for multiple, locus-specific drug delivery to the disease locus as their tiny size can effectively penetrate across obstacles through small capillaries into individual cells. small DDS can circulate freely even in capillaries and are intrinsically better at traversing biological barriers than larger DDS. Drug delivery nanomediated systems are based on biocompatible nanocarriers, such as gold nanoparticles, carbon nanotubes, nanovesicles, micellar systems and dendrimers. Among these, AuNPs has peaked interest in drug delivery research due to their unique properties including cytocompatibility, stability, ease of synthesis, the ability to manufacture a range of sizes and ease of binding with biomolecules.

There are various strategies for using gold nanoparticles as a drug delivery vehicle, including systems based on covalent binding, drug encapsulation, electrostatic adsorption, and other non-covalent assemblies.

In this review, we will introduce the latest achievements in the applications of gold nanoparticles as drug delivery tools for the therapy of human diseases.

2. GOLD NANOPARTICLES FOR ANTIBACTERIAL THERAPY

Conjugates of Au NPs with drug molecules play a vital role in the therapy of various diseases. It helps to improve drug efficacy. The drug is able to directly conjugate with Au NPs via ionic or covalent bonding, or by physical absorption. Early work by Gu et al. reported stable water soluble vancomycin (Van)-covered gold nanoparticles as polyvalent inhibitors and demonstrated their effectiveness towards various enteropathogenic strains (including vancomycin-resistant ones), such as vancomycin-resistant *strains* (VRE) and Gram-negative bacteria [5].

Rai et al. used cefaclor (a second-generation cephalosporin antibiotic) to prepare conjugate with AuNPs. They synthesized 22-52 nm spherical gold nanoparticles using cefaclor at different temperatures. Ii contains a single amino group which acts as the capping agent as well as reducing agent in the synthesis of the gold nanoparticle conjugates. These hybrid structures showed no signs of aggregation, were stable enough to be purified via dialysis, and thus could be properly characterized, indicating the usefulness of an amine–gold binding motif. The conjugates displayed an increased bactericidal activity compared to free cefaclor in both gram-positive and gram-negative bacteria, and they showed lower degradation over time than the free antibiotic drug [6].

Rosemary et al. made a complex of ciprofloxacin and gold nanoshells. Drug delivery research regarding the conjugate was conducted employing *E. coli* DH5R and *L. lactis* MG 1363 using the agar dilution method, results being compared to those of free ciprofloxacin. It showcased high antibacterial activity against *E. coli*. Transmission electron microscopy studies revealed that the bacterial morphology of drug conjugate treated *E. coli* is unharmed by nanoshell therapy, even if the shells were not observed [7].

In another study, a colloidal gold conjugate of the antileukemic drug 5-fluorouracil exhibited observable antibacterial and antifungal activities against *E. coli, Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Micrococcus luteus*, *Aspergillus fumigatus* and *A. niger*. The 5FU-colloidal gold complex, obtained by means of the imino (–NH) group, was assessed using different analytical techniques. The results indicated that the association between anticancer drugs and gold nanoparticles determines a much powerful reaction against Gram-negative bacterial infections [4].

3. GOLD NANOPARTICLES FOR METABOLIC DISEASE THERAPY

Chamberland et al. reported the therapeutic effect of etanercept, an antirheumatic drug, conjugated to gold nanorods. After preparing etanercept-conjugated gold nanorods, ELISA tests were performed in order to validate the conjugation and to indicate that the conjugated anti-TNF-α drug was biologically active. Using photoacoustic tomography they visualized gold nanorods of <1 pM concentration in phantoms or 10 pM concentration in biological tissues, with good signal-to-noise ratio and high spatial resolution, indicating the feasibility of binding TNF (tumor necrosis factor) antagonist pharmaceutical compounds to gold nanorods for the treatment of rheumatitis.

Joshi et al. studied the treatment of diabetes mellitus using hormone insulin functionalized gold nanoparticles. Insulin was load onto bare gold nanoparticles and aspartic acid-coated gold nanoparticles and administered in diabetic Wistar rats by means of both oral and intranasal administration. Much lower blood glucose levels (postprandial hyperglycemia) were noticed when insulin was delivered using gold nanoparticle carriers by intranasal administration. Moreover, the management of the intranasal delivery protocol for postprandial hyperglycemia was similar to that obtained by the conventional subcutaneous administration used for type I diabetes mellitus [8].

4. GOLD NANOPARTICLES FOR CANCER THERAPY

Cancer is a major target of new therapeutics because of the drawbacks associated with current treatment strategies which include large systemic side effects due to the non-specificity of many cancer drugs such as doxorubicin, cisplatin, paclitaxel and tamoxifen. Gold nanoparticles can address some of the side effects in several ways. First, attachment to gold nanoparticles can lead to increased toxicity compared to free drug. This is useful, but must ultimately be combined with increased specificity of the drug conjugate to cancer cells. This can be mediated by passive targeting through enhanced permeability and retention effect (EPR) based on the size of gold nanoparticle conjugates or by active targeting using antibodies or other targeting moieties. In addition, the gold nanostructures themselves can have the ability to kill cells by virtue of intrinsic therapeutic effects such as photothermal effect.

Gold nanoparticles carrying anticancerous drug represent an important class of covalent conjugates (Figure 1).

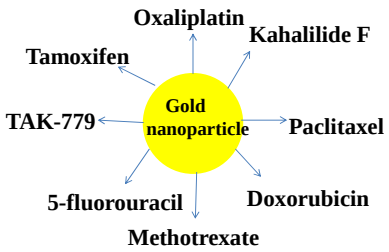

Fig1:Overview of anticancer drugs covalently conjugated to gold nanoparticles

Chen et al. synthesized a 13 nm colloidal Au combined to methotrexate. The drug can restrict the proliferation of cancer cells as it is an analog of folic acid. The carboxylic groups on the methotrexate molecule can combine to the surface of Au NPs after overnight incubation. At the same volume, it has been indicated that the concentration of the methotrexate bound to Au NPs is higher than that of the absence of Au NPs.

Aryal et al. conjugated doxorubicin with AuNPs and the studies in mammary carcinoma and mouse fibroblast cell lines showed their potential to delivering this anticancer drug. Wheate et al. attached the active ingredients of the anticancer drug oxaliplatin to Au NPs for improved drug delivery. The platinum-tethered gold nanoparticles were tested for cytotoxicity, drug intake, and localization in the A549 lung epithelial cancer cell line as well as in the HCT116, HCT 15, HT29, and RKO colon cancer cell lines. The platinum-tethered nanoparticles revealed as good as, or markedly better, cytotoxicity than single oxaliplatin in all of the cell lines, in addition to a unique ability to penetrate the nucleus in the lung cancer cells.

Bowman et al. showed that GNP complexes involving TAK-779 display a more pronounced activity against HIV than the native preparation at the cost of the high local concentration. The synthesis of SDC-1721, a potent HIV inhibitor TAK-779 fragment, was accompanied by its conjugation to gold nanoparticles of 2.0 nm in diameter. The antiviral activity of nanoparticle conjugates was assessed using ELISA test. TAK-779 proved to inhibit the replication of HIV-1 with an IC50 of 10 nM. The IC50 for TAK-779 against four different CCR5-tropic viral isolates varied between 1.6 and 3.7 nM [9].

Bhattacharya et al. found that Au NPs interact with PEG-amines folic and acid by noncovalent bonds were easily targeted to the folate receptors of cancer cells. The polymer-drug conjugates of folic acid with Au NPs could be utilized for targeted drug delivery.

Another type of anticancer drug that has been successfully conjugated to gold nanoparticles was a polypeptide drug, Kahalilide F. It was suggested that a multilayer coating of the peptide molecules onto the nanoparticles was responsible for the observed increased loading of the drug. The increased cellular uptake of the nanoparticle system led to a higher anticancer activity when compared to the free peptide.

Gibson et al. synthesized well-characterized paclitaxel-functionalized gold nanoparticles. Recently, Mirkin et al. have synthesized oligonucleotide–gold nanoparticle conjugates with paclitaxel in order to increase its solubility in aqueous media The gold nanoparticle–DNA–paclitaxel conjugates were shown to be internalized by the cells and showed increased cytotoxicity compared to free paclitaxel in MTT assays, and even showed toxicity to paclitaxel-resistant cell lines, suggesting that nanoparticle-mediated cell uptake could fight drug efflux in drug-resistant cancers [10].

In another study, gold nanoparticles have been covalently grafted with doxorubicin for treatment of drug-resistant breast cancer. Doxorubicin was attached through a thioctic acid-PEG linker to the surface of 30 nm citrate-capped gold nanorods through a hydrazone group. This type of DOX-Au NP attachment allows for the intracellular triggered release of DOX from the Au NPs once inside acidic organelles. This allowed for a rapid increase in intracellular DOX concentration, thereby enhancing therapeutic effects in drug-resistant tumor cells. Similar effects were observed in the gold nanoparticle–DNA–paclitaxel conjugate. A hydrazone-linked doxorubicin thiol was also attached to small gold nanoparticles (ca. 2 nm diameter) and tested in tumor cylindroids, a three-dimensional in vitro cancer model. This system differed in that nanoparticle surface was engineered to carry a dense negative or positive charge, which was found to have a large effect on nanoparticle uptake in the tumor

cylindroids with positively charged particles having the highest degree of uptake.

El-Sayed and coworkers reported the first example of covalent coupling of tamoxifen to gold nanoparticles by attaching it to a thiolated PEG linker .This tamoxifen–PEG–thiol was added to citrate capped particles, which showed 2.7 times higher potency than that of free tamoxifen. This was shown to be a consequence of the increased cellular uptake rate of the nanoparticle–drug complex compared to free tamoxifen and was not due to any multivalency effects, such as those discussed for antibiotic–gold nanoparticle complexes. Particle uptake was mediated by binding to estrogen receptors, which are overexpressed in 75–80% of breast cancers, suggesting that this strategy could be used to selectively target breast cancers compared to regular cells.

Another interesting example of anticancer drug that has been conjugated to gold nanoparticles is 5-fluorouracil, a drug which inhibits DNA and RNA synthesis. Agasti et al. synthesized fluorouracil-functionalized gold nanoparticles of 2 nm size. Irradiation of nanoparticles with 365 nm UV light resulted in controllable release of the drug, which exerted its cytotoxic effect only when it was released from the particle surface. The lack of toxicity of the conjugates before the photo-induced release of the ligand could be very beneficial for targeted treatment of cancer in vivo in cooperation with the passive targeting mechanism (EPR effect)[11].

Recently, Astra Zeneca in partnership with Cytimmune has focused on AuNPs-based nanomedicine in cancer treatment. The PEGylated (polyethylene glycol) colloid gold particles based product, Aurimune (CYT-6091)11 whose nontoxicity has been declared is under current clinical trials. It can efficiently deliver the tumor necrosis factor alpha (TNFα) to tumor sites. Additionally, numerous other AuNPs-based chemotherapy mediators such as Auroshell are striving for success in clinical trials [12].

The literature reviewed till now is limited to invitro testing of the AuNP-drug conjugate. Evidently, for such systems to be effective in cancer treatment, gold nanostructures must be targeted to cancer cells and avoid accumulation in healthy tissue. The system could be effective in vitro but may lose its activity in vivo conditions. Emphasis also needs to be laid on the accumulation of particles in the other parts of the body. Accumulation is commonly seen in the liver, spleen, and kidneys, which are functioning to clear the gold nanoparticles from the body, but can also occur in other areas including the brain and lungs, which may or not be desirable. The effect of imperfect delivery of particles functionalized with toxic anticancer drugs also needs to be analyzed. Understanding the clearance and any long-term nanoparticle toxicity, will be necessary before their clinical application.

5. CONCLUSION

Despite the increasing sophistication of experimental efforts to measure, design and optimize the structure and dynamics of optimum DDS design solely on the basis of experimental research is highly improbable. Another challenge in DDS development is that many DDSs show promise in vitro but fail in vivo. This is mainly because of the lack of mechanistic insight obtainable by experiments which are based on trial and error. Systematic studies evaluating the factors that govern the in vivo performance, in particular the in vivo fate of DDSs, are necessary to further guide the design and development of the next generation AuNPs based DDSs. It is expected that enhancing in vivo targeting of nanoparticle–drug conjugates and understanding their biodistribution will be highly important. Just as importantly, understanding and learning how to control the intracellular fate of nanoparticles will be necessary for further development in this field.

REFERENCES

[1] Iravani, S., "Bacteria in Nanoparticle Synthesis: Current Status and Future Prospects", *International Scholarly Research Notices*, 2014, doi:10.1155/2014/359316.

[2] Dhillon, G.S., Brar, S.K., Kaur, S., and Verma, M., "Green approach for nanoparticle biosynthesis by fungi: current trends and applications", *Critcal Reviews in Biotechnology* 32, 2012, pp.49-73.

[3] Gericke, M., and Pinches, A., "Microbial Production of Gold Nanoparticles", *Gold Bulletin*, 39, 2006, pp.22-28.

[4] Vigderman, L., and Zubarev, E.R., "Therapeutic platforms based on gold nanoparticles and their covalent conjugates with drug molecules", *Advanced Drug Delivery Reviews*, 65, 2013, pp.663–676.

[5] Gu, H., Xu, K., Xu, C., and Xu, B., "Biofunctional magnetic nanoparticles for protein separation and pathogen detection", *Chemical Communications*, 2006, pp.941-949.

[6] A. Rai, A. Prabhune, C.C. Perry, Antibiotic mediated synthesis of gold nanoparticles with potent antimicrobial activity and their application in antimicrobial coatings, J. Mater. Chem. 20 (2010) 6789–6798.

[7] Rosemary, M., MacLaren, I., and Pradeep, T."Investigations of the antibacterial properties of ciprofloxacin@ SiO2". *Langmuir*, *22*, 2006, pp.10125-10129.

[8] Ramezanpour, M., Leung, S.S.W., Delgado-Magnero, K.H., Bashe, B.Y.M., Thewalt, J., and Tieleman, D.P., "Computational and experimental approaches for investigating nanoparticle-based drug delivery systems", *Biochimica et Biophysica Acta* ,1858 ,2016, pp.1688–1709.

[9] Kong, F-Y., Zhang J-W., Li, R-F., Wang, Z-X., Wang, W-J., and Wang, W., "Unique Roles of Gold Nanoparticles in Drug Delivery, Targeting and Imaging Applications", *Molecules*,22, 2017, pp.1-13.

[10] McNamara, K., and Tofail, S.A.M., "Nanoparticles in biomedical applications", *Advances in Physics*: *X*, 2, 2017, pp.54-88.

[11] Cai,W., Gao, T., Hong, H., and Sun, J., "Applications of gold nanoparticles in cancer Nanotechnology", 1, 2008, pp.17-32.

[12] Farooq, M.U., Novosad , V., Rozhkova, E.A., Wali, H., Ali,A., Fateh,A. A., Neogi, P.B., Neogi, A., and Wang, Z.,"Gold nanoparticles-enabled efficient dual delivery of anticancer therapeutics to HeLa cells", *Scientific Reports*, 8 ,2018, 2907.