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Synthesis, Limitation and Application of Gold Nanoparticles in Treatment of Cancerous Cell

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Abstract- It is now generally believed that personalized medicine is the future for cancer patient management. Possessing unprecedented potential for early detection, accurate diagnosis and personalized treatment of cancer, nanoparticles have been extensively studied over last decade. Due to the remarkable properties of gold nanoparticles, they have long been considered as a potential tool for diagnosis of various cancers and for drug delivery applications. These particles have been widely used in various biomedical applications and drug delivery systems due to their inert nature, stability, high dispersity, non-cytotoxicity and biocompatibility. The future looks brighter than ever yet many hurdles remain to be conquered. A multifunctional platform based on gold nanoparticles, with multiple recptor targeting, multimodality imaging, and multiple therapeutic entities, holds the promise for a better treatment against cancer.

Keywords: Nanoparticles, Cytotoxicity, Biocompatibility.

I. INTRODUCTION

Cancer is the third leading causes of death in developed and developing countries after second leading cause of death i.e heart attack in the United States [1]. Cancer is a disease state caused by abnormal cell growth and according to the World Health Organization (WHO), cancer caused 8.8 million deaths in 2015. Current cancer treatment is based on chemotherapeutics drugs, usually involving chemo or radiation therapy, with the aim to kill the cancerous cells [2, 3]. However, there are often several side effects from these treatment due to the damage caused to the surrounding healthy tissues. Treating cancer cells by utilizing a nanoparticle-based drug delivery approach plays a key role in overcoming of conventional treatment methodologies by providing simultaneous diagnosis and treatment [4].

Nanotechnology, an interdisciplinary research field involving chemistry, engineering, biology, and medicine, has great potential for early detection, accurate diagnosis, and personalized treatment of cancer [5]. Nanoparticles are typically smaller than several hundred nanometers in size, comparable to large biological molecules such as enzymes, receptors and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells, which may revolutionize cancer diagnosis and treatment. The most well studied nanoparticles are, Carbon nanotubes, Quantum dots, and Paramagnetic nanoparticles, Liposomes, Gold Nanoparticles and many others [6]. One of the major applications of nanotechnology is in biomedicine. Nanoparticles can be engineered as nanoplat forms for effective and targeted delivery of drugs and imaging labels by overcoming the many biological, biophysical, and biomedical barriers. For in vitro and ex vivo applications, the advantage of state-of-the-art nanodevices (eg, nanochips and nanosensors) over traditional assay methods is obvious [7, 8]. However, there are several barriers exist for in vivo application in preclinical and potentially clinical use of nanotechnology, among which are the biocompatibility, in vivo kinetics, tumour targeting efficacy, acute and chronic toxicity, ability to escape the reticulloendothelial system (RES), and cost-effectiveness [9, 10].

II. GOLD NANOPARTICLES

Properties of gold nanoparticles are different from its bulk form because bulk gold is yellow solid and it is inert in nature while gold nanoparticles are wine red solution and are reported to be anti-oxidant. Inter particle interactions and assembly of gold nanoparticles networks play key role in the determination of properties of this nanoparticle [11]. Gold nanoparticles exhibit various sizes ranging from 1 nm to 8 µm and they also exhibit different shapes such as Decahedral, Spherical, Sub-octahedral, Octahedral,

Icosahedral multiple twined, Irregular shape, Tetrahedral, Nanotriangles, Nanoprisms, Hexagonal platelets and Nanorods [12].

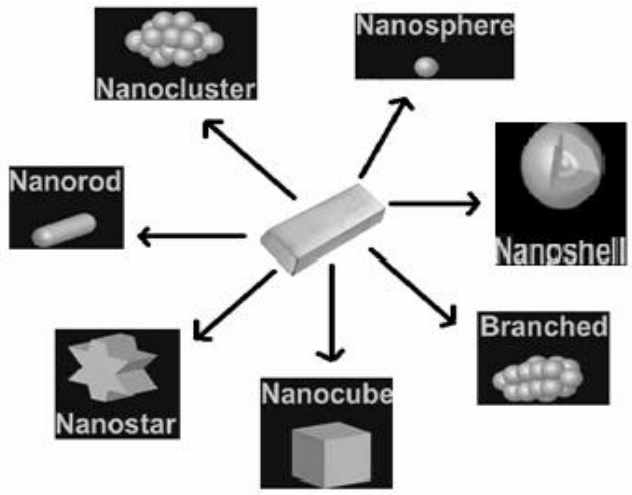

Figure 1: Various shapes of gold nanoparticles

III. DRUG DELIVERY

Several studies have reported the use of gold nanoparticle as drug delivery vehicles. Tumor necrosis factor-alpha (TNF-α), a cytokine with excellent anticancer efficacy, is systemically toxic which severely limited its therapeutic applications [13, 14]. A nanoparticle delivery system, consisting of PEG coated gold nanoparticles loaded with TNF-α, was constructed to maximize the tumour damage and minimize the systemic toxicity of TNF-α [15]. Combination of local heating and nanoparticle-based delivery of TNF-α resulted in enhanced therapeutic efficacy than either treatment alone. Thermally-induced tumour growth delay was enhanced by pre-treatment with the nanoparticle, when given intravenously at the proper dosage and timing. Tumour blood flow suppression, as well as tumour perfusion defects, suggested vascular damage-mediated tumour cell killing. Surprisingly, following intravenous administration, little to no accumulation in the RES (e.g., liver and spleen) or other healthy organs of the animals was observed [16].

Methotrexate (MTX), which has been used to treat cancer form past many years, upon conjugation with gold nanoparticles showed higher cytotoxicity towards numerous tumour cell lines as compared to single use of Methotrexate (MTX). Methotrexate was observed to accumulate in the tumour cells at a faster rate and to a higher level when it is used in conjugation with gold nanoparticles [17]. Another drug named, Doxorubicin (DOX), when bound to gold nanoparticles via an acid labile linker, showed enhanced toxicity against the multi drug resistant MCF-7/ ADR breast cancer line, thus overcoming the multi drug resistance to some extent due to the enhanced uptake of the gold nanoparticle-tethered drug followed by its responsive release within the cell [18]. In the past, peptide-drug conjugates (PDCs) have been investigated for their use as anticancer agents [19, 20, 21, 22]. However, their stability in the blood, liver and kidneys pose a significant challenge to their successful use as an anticancer molecule.

Table 1: Anti-tumor applications of gold nanoparticles in drug delivery.

Nanoparticle	Nanoparticle Size (nm)	Outcome	Cell Lines	Reference
MTX-AuNP	8-80	Higher cutotoxicity towards numerous cell lines as compared to free MTX. Suppression of tumor growth with MTX-AuNP but not with free MTX.	Lewis Lung Carcinoma (LL2) Cells	[23]
DOX-Hyd@AuNP	30	Enhanced toxicity against multi drug resistant cancer cells.	MCF-7/ ADR Cancer Cells	[24]
(Pt(R,R-dach))-AuNP	26.7	Platinum-tethering exhibited higher cytotoxicity as compared to free oxaliplatin that could enter the nucleus	A549 lung epithelial cancer cell line, HCT116, HCT15, HT29, and RKO colon cancer cell lines.	[25]
Tfpep-AuNP conjugated with photodynamic pro-drug Pc 4	5.1	Cellular uptake of targeted particles was significantly higher than that of the non-targeted ones.	LN229 and U87 human glioma cancer lines	[26]
CPP-DOX-AuNP	25	Higher cell death as compared to previously tested 41 nm AuNP	HeLa cells and A549 cells.	[27]
FA-Au-SMCC-DOX		Enhanced drug acuumulation and retention as compared to free DOX in multi drug resistant cancer cells.	Hep G2-R, C0045C, and HDF	[28]
FA-BHC-AuNP	20-60	Increased efficacy of BHC against cancer cells.	Vero and HeLa	[29]
Au-P(LA-DOX)-b-PEG-OH/ FANP	34	Enhanced cellular uptake and cytotoxicity against cancer cells.	4T1 mouse mammary carcinoma cell line.	[30]
DOX@PVP-AuNP	12	Induction of early and late apoptosis in lung	A549, H460 and H520	[31]

		cancer cells and upregulation of tumor suppression genes.	human lung cancer cells.	
DOX-BLM-PEG-AuNP	10	Enhanced half-maximal effective drug concentration, providing rationale for chemotherapy using two drugs.	HeLa cells	[32]
EpCam-RPAuN	48	The biomimetic nanoparticle loaded with PTX was used in combination treatment (PTT and Chemotherapy).	4T1 mouse mammary carcinoma cell line.	[33]

IV. SYNTHESIS STRATEGIES

General methods for the synthesis of gold nanoparticles include Chemical, Physical and Biological Methods.

Chemical Methods

In this method we can synthesize gold nanoparticles supported on an insoluble thiolated chitosan derivative by reduction of the $HAuCl_4$ through chitosan (QTDT) as reducing and coupling agent for gold nanoparticles so the synthesized QT/Aunano is used as a good catalyst for the reduction of methylene blue [34]. Citrate thermo reduction methods was used for the synthesis of gold nanoparticles having efficient SERS (Surface Enhanced Raman Spectroscopy) in short reaction time by using a low cost reagent insoitol hexaphosphate (IP6) as reduction agent for the $HAuCl_4$ [35]. Another method used for the synthesis of thermo-sensitive gold nanoparticles was reported. In this method gold nanoparticles was reduced by the trisodium citrate which was combined with hydrogen tetrachloroaurate (III) tetrahydrate (Chloroauric acid) and modified with 11-mercaptoundecanoic acid (MUA) by the self-assembly monolayers (SAM) [36].

Physical Methods

The γ-irradiation method was proved to be best for the synthesis of gold nanoparticles with controllable size and high purity. The γ-irradiation method is adopted to synthesize gold nanoparticles with size 5-40 nm. In this method natural polyscharride alginate solution was used as stabilizer[37]. Single step γ-irradiation methods has been adopted to synthesized gold nanoparticles of size 2-7 nm by using bovine serum albumin protein as stabilizer [38]. Gold nanoparticles are synthesized via photochemical synthetic approach. In this method, $HAuCl_4$ and aqueous glycine solution was exposed to UV-irradiation. Basically amino acid capped gold nanoparticles were used as photochemical initiator which is then further functionalized with glycine [39].

Green Methods

Green chemistry synthesis routes are environment friendly and non-toxic. A facile green biosynthesis method for the preparation of gold nanoparticles of size 25+7 nm was reported by using natural biomaterial egg shell membrane (ESM). In this method ESM was immersed in aqueous solution of $HAuCl_4$ without using any reductant [40]. Another green synthetic approach was developed to synthesized gold sononanoparticles of size 5-17 nm by using high-power ultrasounds and sodium dehydrate [41].

Gold nanoparticles were successfully synthesized by adopting sun light irradiation method and were modified with folic acid and capped by 6-mercaptopurine. In the method solar energy was used to reduce the gold salt [42]. A new green chemistry method for the preparation of gold nanoparticles were formed in aqueous NaCl solution from the bulk gold substrate by natural chitosan without using any external stabilizer and reductant [43]. Gold nanoparticles of size 15-80 nm are also synthesized via another green synthetic route. In this method $HAuCl_4$ was reduced by using citrus fruits juice extracts (*Citrus limon, Citrus reticulate and citrus sinensis*) [44]. Edible mushroom was also used for the synthesis of gold nanoparticles via sunlight exposure [45].

V. CURRENT LIMITATIONS

Toxicity

The toxicity of gold nanoparticles to biological systems has always been an issue of concern. Properties of gold nanoparticles such as shape, size, surface chemistry, targeting ligand, elasticity and composition largely influence their toxicity. This, in combination with the complexity and the heterogeneity that exists amongst human cells and tissues, make it challenging to comprehensively probe the effect and response of the biological system to the administration of gold nanoparticles. Surface charge can be influence toxicity of gold nanoparticles, wherein positively charged particles were found to be more toxic than negative or neural particles [46]. Other groups, on other hand, found no toxicity induced by positively charged gold nanoparticles [47] and no toxicity of negatively charged particles [48]. This discrepancy arises due to the unique physiochemical nature of nanoparticles, and no significant standardized assay is currently available that could universally be applied to test the toxicity effect of all nanoparticles. The lack of such robust standardized assays leads to varying interpretations or assumptions that limit nanoparticles administration. Toxicity assay using *Caenorhabditis elegans* (ISO 10872 method) is widely used to assess the effect of nanoparticles on multicellular organisms [49].

Size and Biodistribution

Apart from toxicity assessment, size and biodistribution of nanoparticles are also one of the important factors to be

taken into consideration. Tang et. al., reported increased cytotoxicity of smaller gold nanoparticles (8 nm) coated with reduced glutathione when tested on a human hepatic cell line as compared to that of the larger particles (37 nm) [50]. Rosli et. al., recorded that 50 nm gold nanoparticles exhibited higher cytotoxicity in a breast cancer cell line as compared to their 13 and 70 nm counterparts [51]. Connor et. al., studied the cytotoxicity of a series of gold nanoparticles sizes ranging from 4 to 18 nm on human leukemia cells and found that none of the sizes were not harmful to cellular function [52]. Liang et. al., recorded that PEG-coated gold nanoparticles of 4.8 nm had the highest toxicity effect on Hela cells whereas 12.1 and 27.3 nm counterparts showed low toxicity and the 46.6 nm counterpart exhibited absolutely no toxicity [53]. Li et. al., however reported that regardless of the size of the nanoparticles, the observed cytotoxicity was due to dose-dependency [54].

VI. RECENT ADVANCE IN CLINICAL TRAILS

A very few clinical trails are being actively carried out for gold nanoparticles approval in cancer diagnostics and therapy. According to current literature, the FDA has approved few gold nanoparticles-based technologies for diagnostic and therapeutic purpose in medicine [55, 56]. The cytotoxicity of gold nanoparticles is highly dependent on the size and morphology of the particles, environmental scenario, and the method of production [57, 58, 59]. One of the clinical trails being carried out by Astra Zeneca in partnership with Cytimmune mainly focuses on gold nanoparticle-based cancer treatment. Their first phase of trials was successfully completed. Aurimune (CYT-6091) was used as a vehicle to deliver the recombinant human tumor necrosis factor alpha (rhTNF) into tumors, which disrupted the blood vessels, enabling chemotherapeutic drugs to penetrate the tumor and damage the cancer cells. Safe delivery of highly effective doses of rhTNF to tumor cells was observed [60]. They also founded that the doses of the rhTNF administered after immobilization to gold nanoparticles could be three times higher than its usual dose without any toxic effect [61]. The PEG layer also decreased the uptake of nanoparticles by the mononuclear phagocytic system (MPS) and aided in their accumulation in the tumor masses via the EPR (Enhanced Permeation and Retention) effect.

Due to the favourable ability of gold nanoparticles to absorb NIR-Light (Near Infra-Red), interest towards PTT (Photothermal Therapy) has increased. Researchers are mainly focusing on the photothermal conversion efficiencies, selective targeting of cancer cells, enhanced cancer cell destruction, and in vivo bio-distribution of the nanoparticles [62]. For example, Aurolase, developed by Nanospectra, are silica-gold nanoshells coated with (poly) ethylene glycol (PEG) and are designed to thermally ablate the solid tumors following stimulation with a NIR light source. The absorption of light leads to an increase in the local temperature, which thermally dissolves the solid tumors [63].

Table 2: Lists of clinical trials of gold nanoparticles [64]

Name	Materials	Application	Clinical trials.gov Identifier
AuroLase	Silica-gold nanoshells coated with PEG	Laser responsive thermal ablation of solid tumors: head/ neck cancer, primary and/ or metastatic lung tumors	NCT00848042 NCT01679470
AuroLase	Silica-gold nanoshells coated with PEG	Prostate, head and neck, lung MRI/ US fusion imaging and biopsy in combination with nanoparticle-directed focal therapy for ablation of prostate tissue.	NCT02680535
NU-0129	A Spherical Nucleic Acid (SNA) Gold Nanoparticle	Targeting BCL2L12 in recurrent glioblastoma multiforme or gliosarcoma patients	NCT03020017
Silica-Gold Nanoparticles	Silica-Gold Nanoparticles	Plasmonic photothermal therapy of flow-limiting atherosclerotic lesions	NCT01270139
CNM-Au8	Gold nanocrystal	Evaluation of safety, tolerability, and pharmacokinectics of CNM-Au8 in healthy male and female volunteers	NCT02755870
Gold Nanoparticles	Gold nanoparticles	Sensors functionalized with gold nanoparticles, Organic functionalized gold nanoparticles, Detection of gastric lesions.	NCT01420588
Gold Nanoparticles	Gold nanoparticles	Exhaled breath olfactory signature of pulmonary arterial hypertension	NCT02782026

VII. ADVANTAGES OF GOLD NANOPARTICLES

Gold nanoparticles mediated drug delivery systems have many advantages over other nanocarriers as well as to conventional drugs. Gold nanoparticles have been widely used as a cancer antigen and in tumor therapies [65]. Some advantages are listed below:

1. Gold nanoparticles have unique optical [66], physical and chemical properties [67] due to their size and shape. [68]

2. Gold nanoparticles have high surface area [69] which provide dense drug loading.
3. These particles are biocompatible [70] and are readily available for conjugation with small biomolecules such as proteins, enzymes, carboxylic acid, DNA, and amino acids. [71]
4. Gold nanoparticles have controlled dispersity. [72]
5. Due to small size and unique dispersion they can easily reach to the targeted site with blood flow. [73]
6. They are non-cytotoxic to the normal cells. [74]
7. Gold nanoparticles are easily synthesized by various methods. [75]

VIII. CONCLUSION

In this review, we have highlighted the recent advances in the development and application of gold nanoparticles in cancer diagnostics and treatment. Gold nanoparticles, are easily synthesise, possible control over its shape and size, colloidal stability and the ability to tune the surface chemistry to achieve easy conjugation with biological moieties and make them favourable for biomedical application. Surface and core properties of gold nanoparticles can be easily optimised for individual and multifold applications including molecular recognition, chemical sensing and imaging. With the help of Gold nanoparticles, targeted delivery and programmed release of therapeutic drugs to the specific site can be easily achieved because they can bear high drug load and release it to the specific site through various administration routes and can interact with cancerous cells. Side effects of conventional drugs have been minimized by conjugation with gold nanoparticles and they increase the quality life of patients.

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