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Golden Forms of Nano - Sized Anticancer Drugs

[1]Abdel-Hamid, NM, Bastawy, M A[2] and Nagy, MA[3]

1 Biochemistry Department, Minia University, Minia, Egypt,
2 Chemistry Department Faculty of Science, Beni-Suef, Beni-Suef University, Beni-Suef, Egypt.
3 Chemistry Department Faculty of Science, Beni-Suef, Beni-Suef University, Beni-Suef, Egypt.

1 **Corresponding author:** The Editor in Chief of Archives in Cancer Research (ACR). Dr. Nabil Mohie Abdel-Hamid, Diagnostic Laboratory, Abtal El-Faluga Street, Mit-Gomre, Dakahlia, Egypt.

nabilmohie@yahoo.com

M A, Bastawy30 @ yahoo.com[2]

nagy_bio@yahoo.com[3]

Abstract

This review highlights the unique properties of gold nanoparticles (Au NPs), their historical and recent medicinal uses, their journey in the body, how they pass the biological barriers and pores, ultimately, reach a selective accumulation in cancer cells. To verify the aims of the journey, Au NPs are used in conjugated preparations either with proteins, carbohydrates, lipids or nucleic acids. Au NPs exploit biological pathways to achieve payload delivery to cellular and intracellular targets. Several examples of their forms and the use of targeted nanoparticles in the treatment of many cancers are discussed.

List of Abbreviations: AF-Au NPs: Amine-functionalized gold nanoparticles; Au NPs: Gold Nano particles; BBB: Blood brain barrier; BRB: Blood-retinal barrier, BTB: Blood-tumor barrier; EGFR: Epidermal growth factor receptor, FA: Folic acid; FAR: Folate receptors; GA: Gum Arabic, GNP: Gold Nano particles. GSH: Reduced glutathione; MIMS: Mitochondrial inter-membrane spaces; MPTP: Mitochondrial Permeability Transition Pore. NPC: nuclear pore complex; RES: Reticulo-endothelial system; SiRNAs: Small interfering RNA; SLNs: Solid lipid nanoparticles; TACA: Tumor-associated carbohydrate antigens; TFag: Thomsen–Friedenreich antigen; VDAC: Voltage-dependent anion channel; VEGF: Endothelial Growth Factor; VVOs: Vesiculo-vacuolar organelles.

Introduction

Since the earliest days of civilization, the use of gold in therapy has been a component of the physicians' stock in trade. In the twentieth century, gold complexes were introduced for the treatment for cancer[1]. Gold nanoparticles (Au NPs) have unique physico-chemical properties, including ultra small size from 0.8nm to 200 nm, large surface area to mass ratio, high surface reactivity, chemical inertness, biocompatibility and ease of surface fictionalization[2]. Moreover, Au NPs exhibit additional properties for transporting and unloading specific pharmaceuticals. The gold core is essentially inert, non-toxic, exhibits ease in synthesis and versatility in fictionalization. Furthermore, their photo-physical properties could trigger drug release at remote place[3].

Intra-cellularly, Au NPs easily penetrate the nuclear pores to influence the genetic biochemical processes and can diffuse through the mitochondrial membrane pores to alter the bio-energetics of cells that make Au NPs very helpful in intracellular targeting therapy[2].

Moreover, Au NPs can pass through different biological barriers as skin, blood brain barrier (BBB), blood-tumor barrier (BTB), blood-retinal barrier (BRB) and human placental barrier, that may exhibit new pharmacokinetic properties not known before[4]. Conjugation of Au NPs is really necessary for multiple reasons, firstly, to increase their circulation lifetime, secondly, to prevent or slow their removal by the reticulo-endothelial system (RES), lastly, to prevent their aggregation achieving more stability[5].

Therefore, conjugation of Au NPs in different forms as, proteins, carbohydrates, lipids or nucleic acids facilitates selective cellular targeting. Also, it is important in diagnostic and therapeutic purposes, especially in the field of Nano-cancer management[6].

History of gold therapy

Over 5000 years ago, Ancient Egyptians have used gold for medicinal and healing purposes. Moreover, in 2500 BC, Chinese prepared and used red colloidal gold as the drug of longevity[7]. In the 1900s, surgeons implanted a gold piece under the skin near an inflamed joint, such as a knee or elbow, as a result, the pain would often subside or cease altogether[8]. Recently, after development of Nano-cancer therapy and nanotechnology, the use of gold as nanoparticles for detection and treatment of cancer have been extensively developing[9]. Various applications of gold nanoparticles in therapy are shown in **Fig 1**.

Au NPs are capable of converting light energy into heat that could cause destructive damage to cancer cells through local over heating effects. Accordingly, Au NPs appear to be effective agents for photo-activated cancer therapy and it can be used in vivo to destroy cancer cells and tissues in a non-invasive manner[11].

Journey of Au NPs in the body

Since Au NPs are a hundred to thousand times smaller than a human cell, therefore, nano-scale devices (50 nm or less) can enter cells and the organelles easily through an endocytosis and mostly remain in the endosomes. Hence, Au NPs can interact with DNA, proteins, enzymes and cell receptors extra-cellularly and intra-cellularly[12].

Au NPs and biological barriers

Au NPs and Skin

The skin is structured in three layers: the epidermis, the dermis and the subcutaneous layer. The uptake of metals through the skin is complex, because of both exogenous fac-

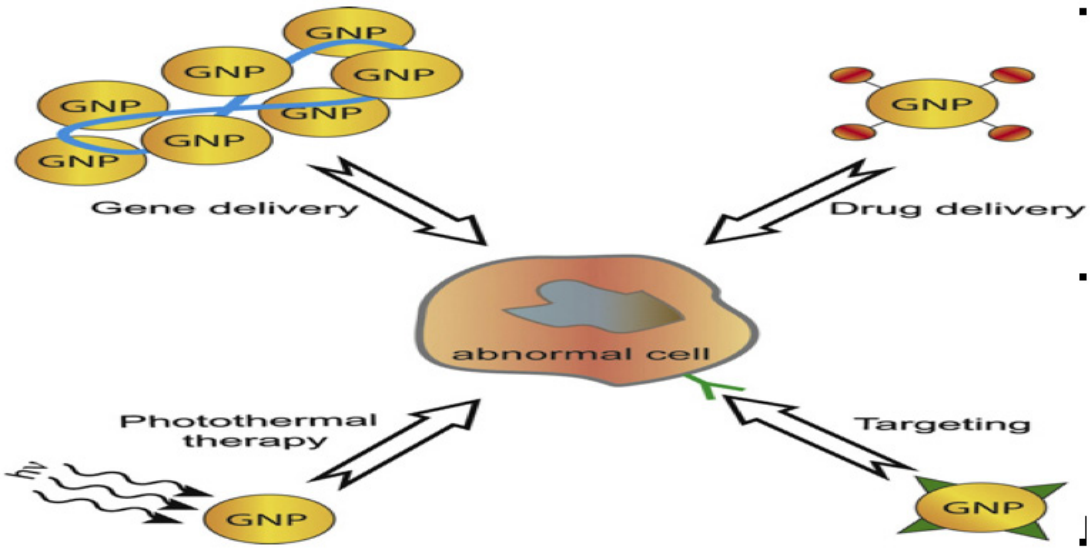

Fig 1. Various applications of gold nanoparticles in therapy[10].

tors (e.g. dose, vehicle, protein reactivity, and valence) and endogenous factors (e.g. age of skin, anatomical site an homeostatic control)[13].

Penetration of the skin barrier is size dependent and Nano-sized particles are more likely to enter more deeply into the skin than larger ones. Also, Au NPs showed size dependent permeation through skin. 15nm gold nanoparticles showed higher permeation compared to 102 nm and 198 nm gold nanoparticles, revealed accumulation of smaller size Au NPs in deeper region of skin whereas larger particles were observed mainly in epidermis and dermis[14].

Au NPs and BBB

BBB restricts the penetration of compounds into the brain through endothelial cells that are closely linked by tight junctions. There is non-saturable uptake of Au NPs across the blood–brain barrier, supporting the possibility to use Au NPs to target the brain without producing detectable toxicity. Hence, treatment and diagnosis of neurodegenerative disorders became more achievable.

In the BTB of malignant solid tumors, the anatomic pore sizes of trans-endothelial cell fenestrations, caveolae and vesiculovacuolar organelles (VVOs) range between 40 nm to 200 nm and the sizes of inter-endothelial cell gaps range between 100 nm and 4700 nm. This may have important implications on the size range of therapeutics that could be effectively delivered across the BTB of malignant solid tumors independent of tumor host site[15].

Au NPs and BRB

The retina maintains homeostasis through blood-retinal barrier (BRB). Au NPs could pass through the BRB and distributed in all retinal layers without cytotoxicity. Au NPs doesn't affect the viability of retinal endothelial cells, astrocytes and retinoblastoma cells. Furthermore, Au NPs doesn't lead to any change in expression of representative biological molecules including zonula occludens-1 and glucose transporters in retinal endothelial cells, neurofilaments in differentiated retinoblastoma cells and glial fibrillary acidic protein in astrocytes[16].

Au NPs and human placental barrier

Little is currently known about whether Au NPs can cross the human placental barrier or interfere with placental function, but suitable transport models have been developed which can be used to clarify the mechanisms of cellular interaction and transport across the placenta[17].

Accumulation of Au NPs in Tumors

Au NPs (≤20 nm) can move out of blood vessels and circulate throughout the body[18]. Au NPs' tumor accumulation is deemed possible due to the highly permeable blood vessels of the tambours as a result of rapid and defected angiogenesis. In addition, the tumors are characterized by dysfunctional lymphatic drainage that helps the retention of nanoparticles in tumor long enough to allow local nanoparticle disintegration and release of the drug in the vicinity of tumor cells[19].

Accumulation of Au NPs in kidney

The accumulation of Au NPs in kidney could be explained by the bigger size of the particle with respect to the glomerular pores that measure 5.5 nm. So it is unlikely that NPs can pass through the glomerular filtration due to its size and negative electrostatic potential[20].

Accumulation of Au NPs in liver

Au NPs are taken up by Kupffer cells in the liver regardless of the particle size[21]. In the liver, the bioaccumulation of Au NPs may be regulated by the reticulo-endothelial system[22]. Au NPs significantly inhibit the angiogenesis and growth of liver cancer cells with the possible mechanism that Nano gold inhibits the VEGF (Vascular Endothelial Growth Factor) -induced signaling[23].

Au NPs and biological pores

Biological protein pores and pore-forming peptides can generate a pathway for the flux of ions and other charged or polar molecules across cellular membranes. In nature, these Nano pores have diverse and essential functions that range from maintaining cell homeostasis and participating in cell signaling to activate or kill cells[24].

Au NPs and Nuclear pores:

Nuclear pores are large protein complexes that cross the nuclear envelope, the entire nuclear pore complex (NPC) has a diameter of about 120 nanometers, the diameter of the opening (functional diameter) is about 9 nanometers wide and its "depth" is about 200 nanometers. It had been suggested that the pore can be dilated to around 26 nanometers to allow molecular passage[25].

Importantly, mono dispersed Au NPs with average size of 3.7 nm can enter the nucleus of HeLa cells with no obvious cytotoxicity, so that provide an important size parameter to devise nanomaterial to carry the biomolecules or drug inside the cells or nucleus[26].

Although the Au NPs are assumed to be safe, it was revealed that more than 30 genes are activated upon exposing living cells to Au NPs and affect the flow of genetic information that is represented by expression of defected proteins. This e effect either on the level of DNA synthesis (replication), RNA synthesis (transcription) or protein synthesis (translation) is still unclear. Questions in need to answers may arise: are we have to obstacle these genetic processes that may affect dangerously other normal cells applying the rule of all or none ? or it is recommended to just slow the rate of these nuclear pathways, that may decrease the invasive cancer progress with little side effects on other normal cells for any designed anticancer therapeutic?

Au NPs and mitochondrial membrane pores

Mitochondrial Permeability Transition Pore (MPTP) is a nonselective protein pore, having high conductance channel with multiple macromolecular components.

Au NPs particles with 3-nm diameter can enter the mitochondrial intermembrane spaces (MIMS) through voltage-dependent anion channel (VDAC). The physical diameter of the VDAC pore is ≥3 nm but ≤ 6 nm. MPTP damages the outer mitochondrial membrane (OMM) and opens it for particles ≥6 nm in size resulting in the release of cytochrome C oxidase, triggering apoptosis[27].

Still unobvious, the biochemical effects of Au NPs of different forms on the metabolic and energy pathways within mitochondria either on the level of carbohydrate, lipid or protein metabolism. Nuclear orders derive mitochondria to accelerate the metabolic pathways for energy production responsible for the crazy growth of cancer cells. Hence, cutting signal pathways between nucleus and mitochondria in cancer cell, will free mitochondria from the control of crazy orders of cancer nucleus and slow or even prevent cancer growth.

Bio conjugation of Au NPs

Generally, there are two types of targeted therapy, designated as 'active' and 'passive'. The term 'active targeting', denotes that the nanoparticle has been conjugated with a specific active molecule that binds to the desired target cells or tissues as tumors. In the case of 'passive targeting' it commonly refers to the accumulation of nanoparticles at a specific site by physiochemical factors (e.g. size, molecular weight), extravasation, or pharmacological factors, as shown in **Fig 2**[28]:

Active targeting may be the best method of choice, provided that it exhibits strong enough stability to reach the desired site after administration. Without the incorporation of targeting ligands, Au NPs rely on non specific interactions with cell membranes29. On other hand, Au NPs' bio conjugates that used in diagnosis or therapy must be nontoxic, biocompa-

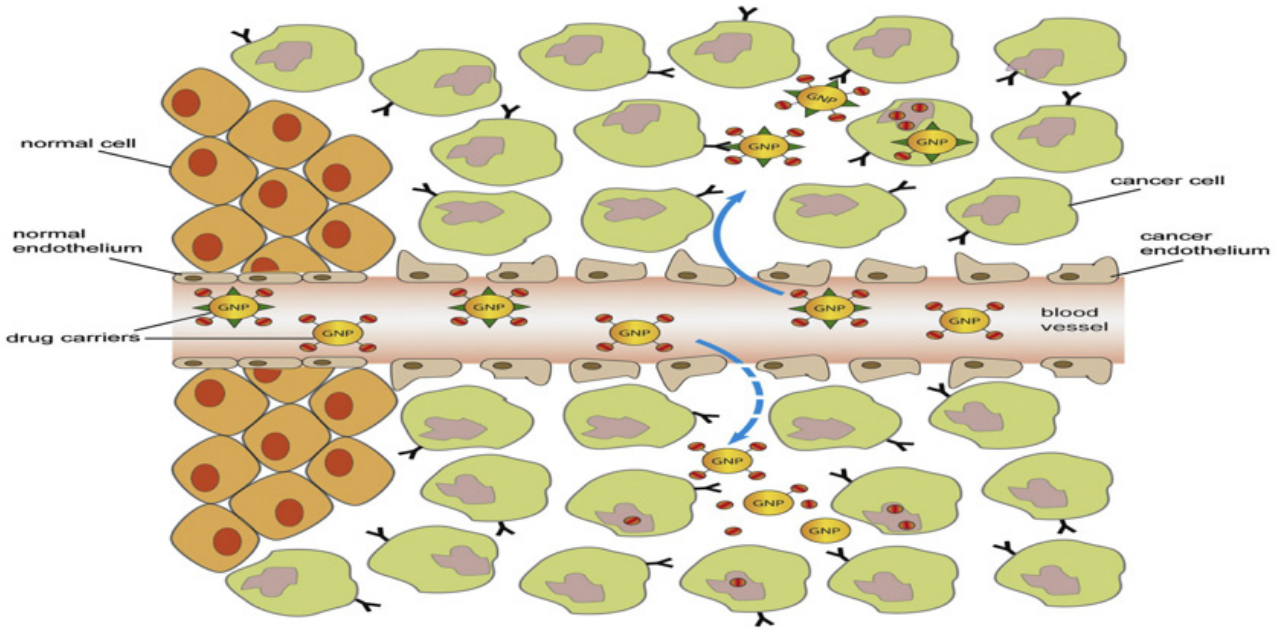

Fig 2. A schematic illustration of drug delivery via 'active' and 'passive' targeting, solid and dotted line respectively

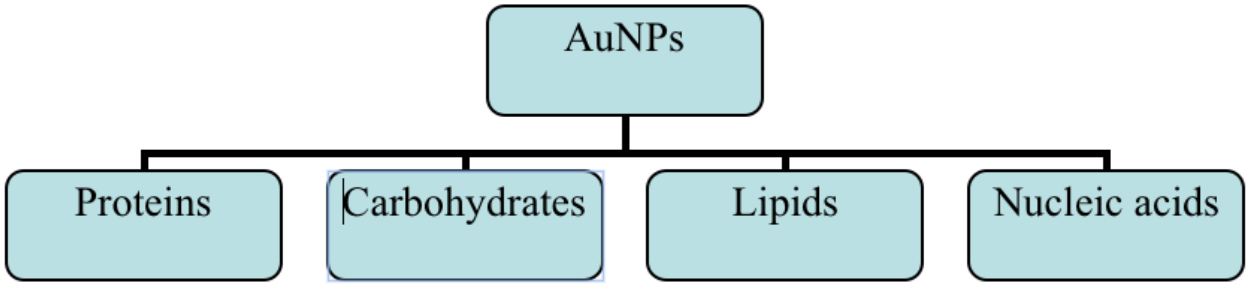

Fig 3. Shows different types of Au NPs bio conjugates.

tible and stable in biological media with high selectivity for biological targets3.

For selectivity and stability of Au NPs during its journey to the desired site, surface modification is important, firstly, to increase the circulation lifetime of the conjugate and prevent or slow its removal by (RE. Another reason is that the desired targeting and therapeutic molecules can be properly attached. Thirdly, to improve the stability of the Au NPs and to prevent their aggregation. Finally, the original capping ligands on some gold nanoparticles (such as gold Nano-rods) may be cytotoxic and it may be necessary to remedy this problem by modifying the surface[30]. Au NPs are usually coated with a layer of hydrophilic and biocompatible polymer such as poly ethylene glycol (PEG)[31]. The use of PEG to modify the surface of gold nanoparticles strongly increases the efficiency of cellular uptake compared to unmodified Au NPs[32]. Bio conjugation of Au NPs may be with proteins, carbohydrates, lipids or nucleic acids as shown in **Fig 3**:

Protein Au NPs bio conjugates

Au NPs' bio conjugates specifically bind to the surface of the cancerous cells with six times greater affinity than to non cancerous cells[33]. The conjugation of one Au NP to a peptide can be carried out by spontaneous reaction of the Au NP surface with a thiol (cysteine) or an N-terminal primary amine[34]. The thiol group is considered as the most important type of molecule to stabilize any size of Au NPs by forming a "staple motif" chemical model: two thiol groups' interacting with three gold atoms in a bridge conformation[35]. The release of the pay loaded drug could be triggered by internal reduced glutathione (GSH)[36] or external e.g. light stimuli[30, 37]. The Nano scale size of these Au NPs' bio conjugates prevents uptake by mononuclear phagocytic cells and allows for their penetration through the smallest capillary pores within the human vasculature. Therefore, the particles bearing anticancer drugs can be delivered in a targeted fashion[38]. Different forms of protein Au NPs' conjugates are listed in **Table 1**:

Folic acid glutathione conjugated Au NPs

It is interesting to know that folic acid receptors (FAR) are up-regulated on a variety of human cancers, including cancers of the breast, ovaries, endometrium, kidneys, colon, brain and myeloid cells of hematopoietic origin. The lack of folate receptors in non proliferating normal cells differentiates them from tumor cells. So, the receptor for folic acid constitutes a useful target for tumor specific delivery, because folic acid (FA) has a high affinity to cell surface receptors. Moreover, it

Table 1. Protein Au NPs bio conjugates.

Ref	Uses	Conjugation
39	Used for targeting and detecting cancer cells.	Folic acid Glutathione conjugated nanoparticles (FA-GSH-GNPs).
40	Used for photo thermal cancer therapy and contrast agent for various imaging modalities (e.g., computed tomography, CT).	a- Folate-conjugated poly (L-aspartate-doxorubicin). b- poly ethylene glycol copolymer.
41	Used as a detector for neuroendocrine tumors.	Au NPs capped by [Tyr3] Octreotide (TOC), known as (Au NP-TOC).
42	Used for detecting prostate, breast, and small-cell lung carcinoma.	Bombesin (BBN) conjugated Au NPs.

is non immunogenic, highly stable, inexpensive and has small molecular size. Thus it facilitates internalization of nanoparticles through cell membrane. Therefore, the development of an efficient gold nanoparticles-folate conjugates[43].

Anti- epidermal growth factor receptor EGFR -conjugated Au NPs

EGFR is one such clinically relevant cell surface receptor that is over expressed in vast majority of epithelial cancer but not in normal cells. EGFR in endosomes can activate growth. Expression of EGFR family members in breast cancer correlates with aggressive tumor behavior and reduced survival time. Its expression is known to correlate with cancer progression in the epithelial origin. Anti- EGFR -conjugated gold nanoparticle holds several clinical implications for early cancer diagnosis, based on molecular specific changes. It could translate into improved ability to detect early dysplastic changes leading to early detection of premalignant lesions and improved diagnosis of cancer and reducing incidence of cancer in high-risk individuals[44].

[Tyr3] Octreotide conjugated Au NPs

The octreotide peptide (OC) is a synthetic somatostatin analogue that specifically targets somatostatin receptors and was developed for the suppression of somatostatin hypersecretion to control neuroendocrine disease symptoms. OC labeled with technetium-99nm (99nmTc-TOC) is currently used as a stable complex to detect neuroendocrine tumors by molecular imaging in nuclear medicine [41].

Bombesin conjugated Au NPs

Bombesin is a 14-amino acid peptide, having two known homologs in mammals called neuromedin B and gastrin releasing peptide. Bombesin is also a tumor marker for small cell carcinoma of lung, gastric cancer, and neuroblastoma. So, Bombesin conjugated Au NPs is used in diagnosis of tumors[45].

Heparin immobilized gold nanoparticles

Heparin, a highly sulfated glycosaminoglycan, has diverse biological functions such as anti-angiogenesis, and proliferative for tumor cell through its apoptosis-inducing activity within cells by interacting with various transcription factors [50]. Therefore Au NP- HHep probes optically detect metastatic cancer cells that over-express heparinase/ heparanase and induces apoptotic death of cancer cells, as illustrated in **Fig 4**:

Chitosan-capped Au NPs

Chitosan is a polysaccharide obtained by heterogeneous deacetylation of chitin. It exhibits a high degree of biocompatibility and low toxicity, with immune stimulating properties and due to its unique poly-cationic character, it quickly binds to negatively charged surfaces such as cellular membranes or anionic Au NPs. Moreover, the amine chemical groups present in its structure makes chitosan able to bind to serum proteins and to recognize specific receptors that are present on various types of cancer cells [51].

Gum Arabic(GA) glycoprotein conjugated Au NPs

Another conjugate is GA. The complex polysaccharides and protein structures within the GA backbone can effectively and irreversibly bind Au NPs on the protein matrix to produce nontoxic gold Nano particulate constructs (GA-Au NPs) that are stable under in vitro and in vivo conditions for potential applications in therapeutic use in Nano medicine [52].

Carbohydrates Au NPs bio conjugates (**Table 2**).

Ref	Uses	Conjugation
46	Used for optical imaging and apoptotic death of cancer cells.	Heparin immobilized gold nanoparticles (Au NP-HHep).
47	Used for cellular imaging or in photo thermal therapy.	Chitosan-capped Au NPs.
48	Used as a Nano construct in prostate tumor.	Gum Arabic glycoprotein (GA) –conjugated (GA-Au NPs).
49	Used for exploring immune response to Thomsen–Friedenreich antigen (TF g).	Thomsen–Friedenreich disaccharide tumor-associated carbohydrate antigen conjugated (TF ag Au NPs).

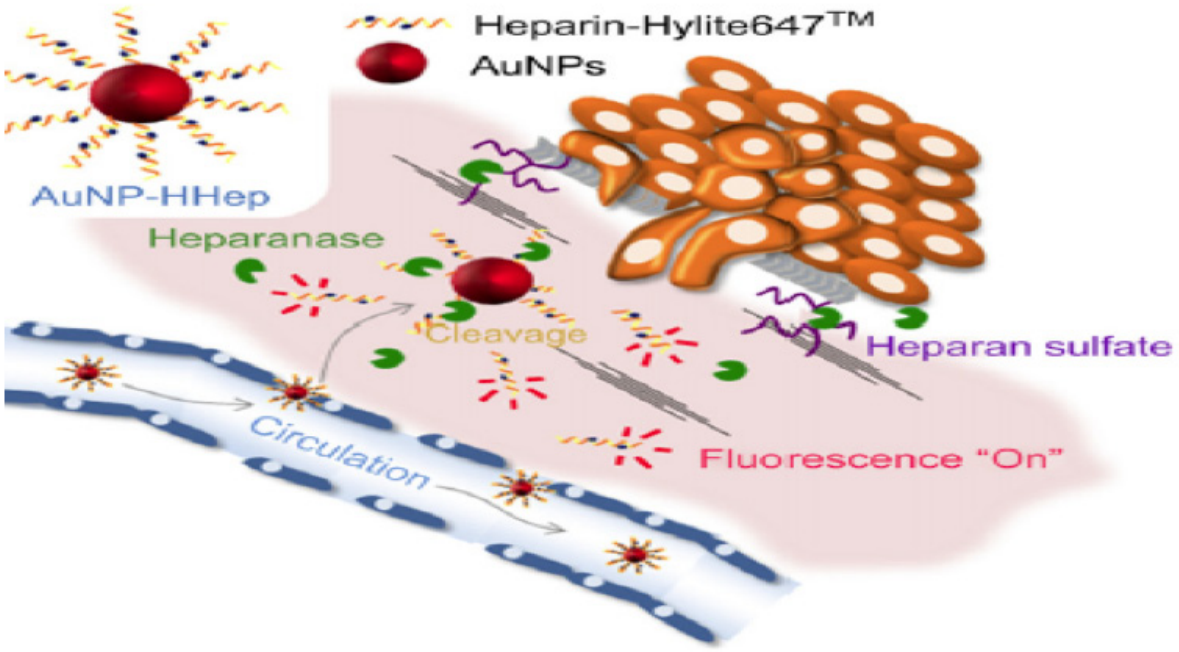

Fig 4. Schematic illustration of heparin-immobilized gold nanoparticles (Au NP-HHep) for metastatic cancer cell detection.

Thomsen–Friedenreich antigen conjugated (TFAg) Au NPs

It is a human tumor-associated carbohydrate antigen present primarily in carcinomas but rarely expressed in normal tissues[53]. TFag-coated GNP could inhibit lung metastasis in the murine 4T1 breast cancer model.

Lipid conjugated Au NPs

Concerning lipid-based systems, it has been established in several laboratories that conjugation of Au NPs with lipid improves their stability and increases their circulation lifetime [54].

Au NPs and Liposomes

Liposome (phospholipid vesicles) are the most established delivery technologies.They consist of a lipid bilayer that envelops an internal aqueous compartment[55]. Incorporation of small Au NPs into or on the surface of liposomes improves the in vivo stability, circulation lifetime, and cellular uptake of Au. Addition of small NPs to the surface of liposomes, results in only minor changes to liposome surface properties and stability. The core of the liposome can be used as a carrier for conventional imaging contrast agents such as iodine and gadolinium or therapeutic agents creating multifunctional systems[56]. Liposomes embedded with gold nanoparticles show light-triggered contents release. For example, the contents released from liposomes with embedded gold nanoparticles were selectively induced with UV light irradiation, whereas liposomes devoid of gold nanoparticles remained unaffected [37].

Solid lipid nanoparticles (SLNs)

SLNs are lipid-based submicron colloidal carriers. They were initially designed in the early 1990s as a pharmaceutical alternative to liposomes and emulsions. They have attracted increasing attention as an efficient and non-toxic alternative to lipophilic colloidal drug carrier prepared either with physiological lipids or lipid molecules used as common pharmaceutical excipients [57]. Under optimized conditions, SLNs can be produced to carry lipophilic or hydrophilic drugs to fulfill the requirements for an optimum particulate carrier system[58]. Their colloidal dimensions and controlled release behavior enable drug protection through administration by parenteral and non-parenteral routes, thus emphasizing the versatility of this Nano particulate carrier.

The conjugated Au NPs based on lipids are generally "soft" and flexible. They can penetrate biological membranes due to their flexibility and biophysical interaction with cellular membrane components[59].

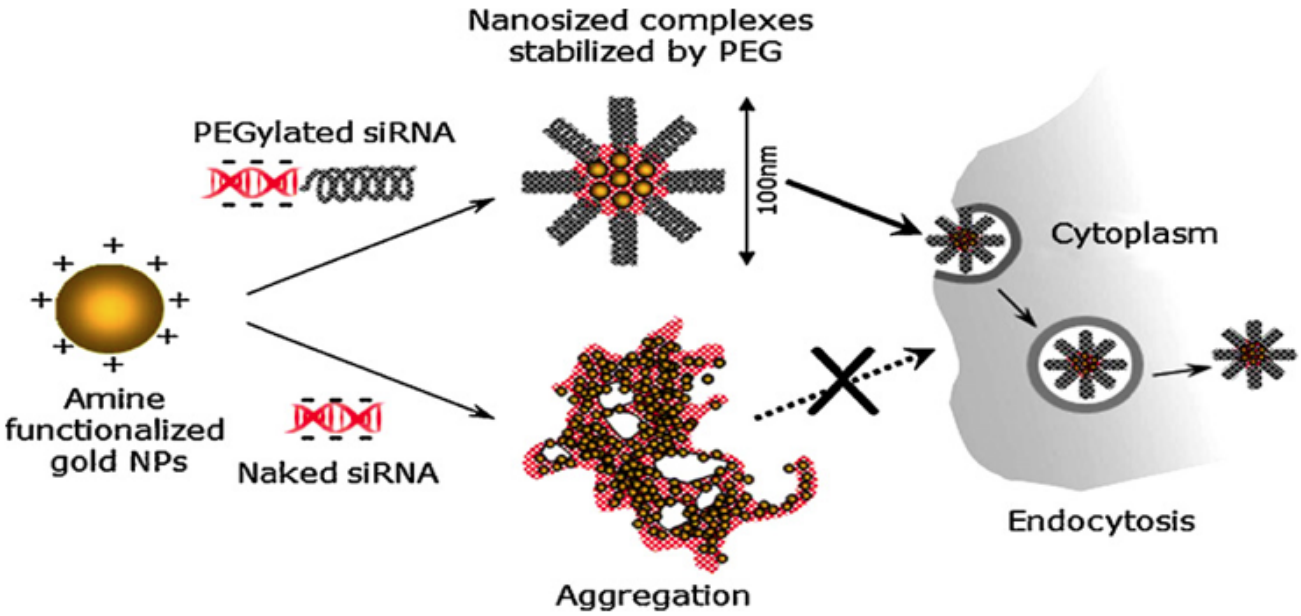

Fig 5. Schematic illustration for polyelectrolyte complexes formed from amine-functionalized gold nanoparticles (AF-Au NPs) with siRNA and siRNA–PEG conjugate [63].

Small interfering RNA (siRNAs) conjugated Au NPs

SiRNA is a poly-anion and hydrophilic molecule which can not freely cross the lipid bilayers of the cell membrane. Introduction of unmodified and non vectored siRNA in cell culture normally results in unsuccessful knock down of the target gene, since mammalian cells appear to lack the effective ds-RNA uptake machinery [60]. Chemically modified Au NPs with primary and quaternary amine moieties were ionically interacted with plasmid DNA, and exhibited more efficient intracellular delivery than the conventional transfection agents [61]. Conjugated Au NPs with siRNA induce sequence-specific degradation of complementary mRNA, leading to knock down of a target protein in post-transcriptional level, as shown in **Fig 5** [62]:

Conjugated Au NPs with siRNA may be used for treating various diseases such as cancer, due to their superior ability to silence target genes in a specific manner [64].

Conclusion and future outlook

Here, we present an overview of the clinically used Au NPs for imaging and treatment of cancer. There are several types of conjugated Au NPs currently at an early design step that may progress in the future to preclinical development for cancer imaging and therapy. Some questions need answers: Biochemical effects of conjugated Au NPs on biological pores importantly nuclear pores, related effects on flow of genetic information, mitochondrial pores or flow of metabolic steps in response to nuclear orders. Evaluation of both genetic and energy pathways is important either for cancer imaging and to predict the coming information from cell nucleus or physiological response from mitochondria that participate in developed stages of cancer initiation. Hence, one may prevent, delay initiation or fasten the termination process of cancer growth, taking into consideration, biochemical effects of conjugated Au NPs and mechanisms by which it disrupts the communication and balance between nucleus informatics and mitochondrial metabolic responses. Many Nano organic forms are being tried for its utility in cancer management which still need perspective research to make it more pronounced in drug markets.

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