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GOLD NANO PARTICLES OF CANCER TREATMENT: A REVIEW

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ABSTRACT

Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photothermal agents, contrast agents and radiosensitisers. Cancer is the disease caused by an uncontrolled division of abnormal cells in a part of the body.In this review some various nanotechnology is found the 10 new technique and treated with all the cancer treatment is beneficial compare to other cancer therapy.Will the synthesis of various gold nano particles and find out the gold nano shells, gold nano cages, gold colloidal nano spheres. Then Nanoparticles can be used to target bio markers or antigens that are highly specific to Cancer cells.This gold nano particles using the therapy Rheumatoid arthritis, Alzheimer's disease, Cancer detection. The introduces to the cancer diseases,nano particles techniques, cancer therapy, then various types of the gold nano particles, propertices of cancer cells, future scope of cancer treatment, applications, background of cancer treatment will be discussed.

KEYWORDS: Gold nano particles techniques, cancer treatment, clinical trials.

INTRODUCTION

Goldnanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photothermal agents; contrast agents and radiosensitisers. Nanoparticles are microscopic particles that have at leastone dimension within a scale of 1-100 nanometers. Gives a clearer picture of that scale by comparingthe nanoscale to macroscale objects. The term “nanoparticle” refers to a combination of individual atoms. For example, agold nanoparticle may be made up of 50 individual goldatoms. Contrary to popular belief, nanoparticles are not necessarily spherical in shape. Theycan be rods, pyramids, spheres, or unnamed shapes.Whatever shape they may be, the cluster of particles isdenoted as

one particle because the traits of the nanoparticleas a whole are important in determining properties and reactivity.

Colloidal gold, also known as "nanogold", is a suspension (or colloid) of sub-micrometre-sizedparticles of gold in a fluid — usually water. The liquid is usually either an intense red colour (forparticles less than 100 nm), or a dirty yellowish colour (for larger particles). “Gold nanoparticlesare very good at scattering and absorbing light,” It has scattering property in a living cell to makecancer detection easier.

Many cancer cells have a protein, known as Epidermal Growth Factor Receptor (EFGR), all overtheir surface, while healthy cells typically do not express the protein as strongly. By conjugating,or binding, the gold nanoparticles to an antibody for EFGR, suitably named anti-EFGR. It is ableto get the nanoparticles to attach themselves to the cancer cells. “If you add this conjugatednanoparticle solution to healthy cells and cancerous cells and you look at the image, you can tell with a simple microscope that the whole cancer cell is shining,” “The healthy cell doesn’t bind tothe nanoparticles specifically, so you don’t see where the cells are. With this technique, if yousee a well defined cell glowing, that’s cancer.”

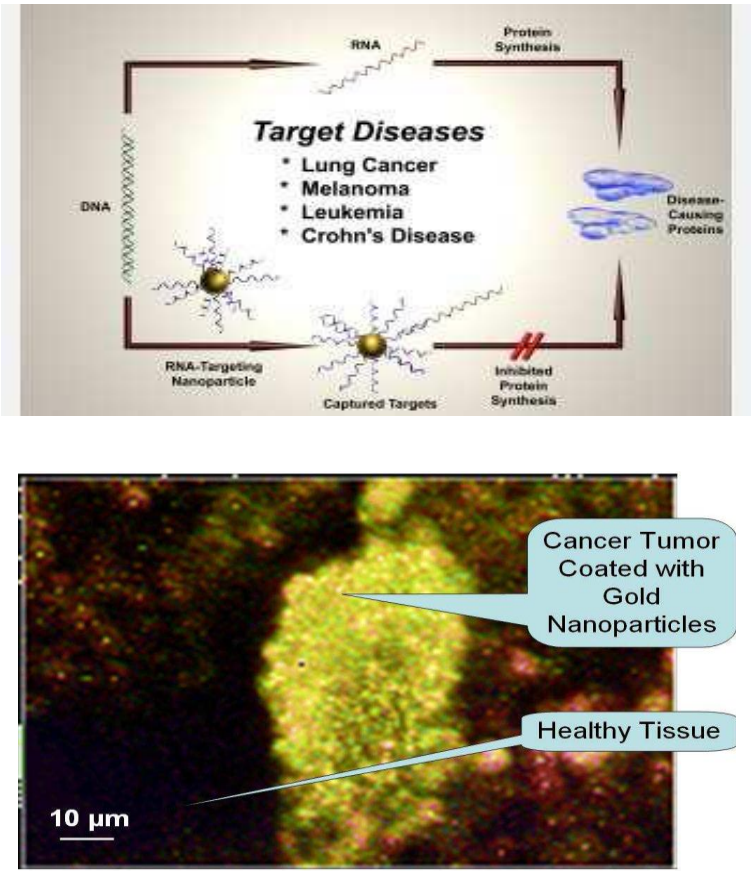

FIG. 1: Cancer Tumor Coated With Gold Nanoparticles.

The gold nanoparticles have 600 percent greater affinity for cancer cells than for noncancerouscells. The particles that worked the best were 35 nanometers in size. Technique using cellcultures of two different types of oral cancer and one nonmalignant cell line. The shapes of thestrong absorption spectrum of the gold nanoparticles are also found to distinguish betweencancer cells and noncancerous cells. Another benefit is that the results are instantaneous. "If you take cells from a cancer stricken tissue and spray them with these gold nanoparticles thathave this antibody you can see the results immediately. The scattering is so strong that you candetect a single particle," Finally, the technique isn't toxic to human cells. A similar techniqueusing artificial atoms known as Quantum Dots uses semiconductor crystals to mark cancer cells,but the semiconductor material is potentially toxic to the cells and humans. "This technique isvery simple and inexpensive to use". It making cacancer detection easier, faster and less.

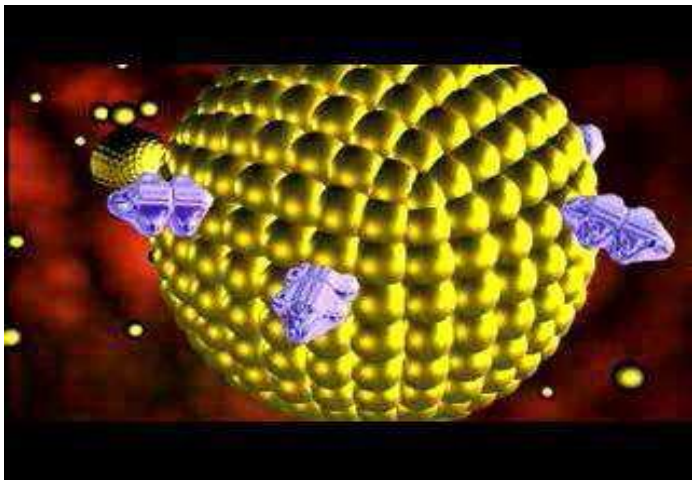

Figure 2. A gold nanoparticle is made of individual gold atoms.

CANCER[2]

- Cancer is the disease caused by an uncontrolled division of abnormal cells in a part of the body.

ADVENTAGES[3,4]

The growing evolution of nanotechnology has opened up doors to scientists demonstrating a vast array of advantageous uses nanotechnology has to offer in the area of medicine. A perfect example is the new concept of using nanorods to detect cancer; this has proved to have numerous positive outcomes compared to flow cytometry, in which fluorescent markers bind to cancer cells. The price of diagnosis compared to that of the method of flow cytometry could be cut by two-thirds just by using nanorods. Where flow cytometry demands a larger

sample size, nanorods only require a fraction of the number of cells, meaning that nanorods are capable of helping to determine an earlier diagnosis. Even more so, nanorods have been proven to be far less invasive compared to some other methods due to the fact nanorods use blood samples and do not require a biopsy. However, it must be taken into consideration that some forms of cancer are not expressed in blood samples and in such cases other methods would be necessary to detect cancer. The added advantage of this is that scientists can use conventional microscopes and light sources to view the samples versus other methods that utilize expensive microscopes or lasers contributes to theoverall cost savings of nanorods.

Protects drugs from being degraded in the body before they reach their target.Enhances the absorption of drugs into tumors and into the cancerous cells themselves. Allows for better control over the timing and distribution of drugs to the tissue, making it easier for oncologists to assess how well they work. Prevent drugs from interacting with normal cells, thus avoiding side effects.

DISADVENTAGES

Yet in recent times growing numbers of scientists have begun to shine a light on the possible concerns that nanoparticles bear and their negative health effects. Nanoparticles are famous for their small size. Due to this, it is possible for nanoparticles to penetrate almost any membrane in the body. Where this is advantageous for cancer treatment, it is a major drawback because of the potential harm to healthy cells and DNA – causing more cancer cells.Careful consideration must also be taken concerning the disposal techniques for nanoparticles used in manufacturing or other processes. It is important that special disposal methods are practiced to stop damaging particles from ending up in the water supply or in the general environment, where they would be impossible to track.

Another potential disadvantage derived from nanoparticles is concerns over the idea of mass poisoning.9 As nanotechnology can be found in almost every food product in the market place, it is a probable idea that the future health effect of this has the potential to be on a large scale. If the coatings contain toxic nanoparticles which are capable of transgressing the blood-brain barrier, they then run the risk of creating mass poisoning.Atomic weapons can now be more accessible and made to be more powerful and more destructive. These can also become more accessible with nanotechnology.

Since these particles are very small, problems can actually arise from the inhalation of these minute particles, much like the problems a person gets from inhaling minute asbestos particles.Presently, nanotechnology is very expensive and developing it can cost you a lot of money. It is also pretty difficult to manufacture, which is probably why products made with nanotechnology are more expensive.

Nanoparticals Techniques[3,4]

1. Liposome Nanoparticles

Lipids form nanoparticle vesicles through the self-assembly of amphiphilic lipidsand excipients. The lipids form a bilayer based on hydrophobic interactions incontinuous parallel packing, with the hydrophilic head groups positioned towardsthe aqueous environment. Hydrophilic molecules can be encapsulated in the inneraqueous phase while hydrophobic molecules can be carried in the hydrophobicdomains of the lipid bilayer. Physicochemical properties of liposomes can beprecisely changed to control surface charge, functionality, and size by simplymixing commercially available lipid molecules. This offers a significant advantageover other carriers that require much more controlled synthesis steps and additionalchemical modifications. Generally, lipids used to prepare vesicular formulations arefound in the human body and approved by the FDA, such as DSPE (1,2-distearoylsn-glycero-3 phosphoethanolamine), HSPC (hydrogenated phosphatidylcholinefrom soybean lecithin), EggPG (egg yolk phosphatidylglycerol) and DSPC(1,2-distearoyl-glycero-3-phosphocholine). Each of these lipids can be obtainedwith or without PEG, which can be used to modify the surface of the resulting liposome.

Doxil, a pegylated liposome clinically used to treat multipleLiposomal formulations have demonstrated multiple benefits as drug deliveryvehicles. However, they must be used to carry very potent drugs due to their lowencapsulated load. Lipid-based vesicles pose several other challenges such asinstability in the bloodstream, poor solubility of many drugs in the lipid/surfactantsolution, and a rapid, burst release of drug. Liposomal formulations are alsoassociated with severe side effects due to their accumulation in skin tissue. While prolonged drug release kinetics are difficult to control using liposomal systems,alternatives such as environmentally triggered release can be easily engineered byinserting destabilizing lipids with amine head groups into the vesicle membrane orincluding additives such as morpholine in the lipid formulation. Thereare currently no liposomal formulations with triggered drug release approved forclinical use or in early phases of clinical trials. However,

LiPlasomePharma developednon-targeted liposomes consisting of lipids designed to be degraded by phospholipaseA2 (PLA2), which is up-regulated in the tumor microenvironment.

The lipid degradation products are converted into anticancer drugs, resulting in local delivery of cytotoxic drugs in the tumor. In-vivo results showed a delay in coloncancer progression using a human tumor xenograft mice model This approach also provides the possibility of multi-drug delivery. Protein stabilizationof liposomesis being investigated by Azaya Therapeutics to deliver hydrophobicdrugs such as docetaxel for cancer therapy. Docetaxel is encapsulated into theliposome bi-layer and stabilized by albumin to prevent rapid drug leakage (ATI-1123). The results of ATI-1123 efficacy studies in human xenograft mice models forprostate, pancreatic, and non-small-cell lung cancer (NSCL cancer) showed partialtumor regression in 90% of the PC3 tumor xenograft model and improved efficacy inthe pancreas model when compared to groups treated with docetaxel at equal doses(25 mg kg_1). This may be explained by the slower plasma elimination and higher.

2. Polymer–Drug Conjugates Nanoparticles

Polymer–drug conjugates are one of the most investigated types of nanocarriers andare currently in clinical trials as advanced as phase III. Polymer–drug conjugatesare formed through side-chain grafting of drugs to polymer chains, allowing themto deliver high doses of chemotherapeutic drugs. Although the physicochemicalproperties of a number of formulations are not disclosed, the size of polymer–drugconjugates is generally below 20 nm. HPMA-doxorubicin (N-(2-hydroxypropyl)methacrylamide) copolymer (PK1) was the first synthetic polymer–anticancer drugconjugate to enter clinical trials more than a decade ago and the clinical phase II trial for women with advanced breast cancer is still ongoing Similarly, Prolindac (AP5346) is composed of a HPMA backbone copolymer withplatinum grafted to the side chains through a pH-sensitive chelator designed fordrug release in the tumor environment. Preclinical data showssuperior efficacy of the polymer–drug conjugates using multiple cancer modelsincluding a M5076 sarcoma platinum-resistant tumor xenograft mice model, multiplecolon xenograft models, L1210 leukemia, and 0157 hybridoma models.

Oxaliplatin drug loading was ~10% (w/w) using a polymer chain of25 kDa and the drug release was slow. Formulations were injected once a week for three weeks and the polymer–drug conjugates significantly retarded tumor growthover one month due to higher intracellular concentration of Pt. In the clinical phaseI trial conducted in Europe, systemic injection of640 mg Pt m_2 weekly for 3 weeks resulted in a response by platinum-

resistantovarian cancer. Recently, Access Pharmaceuticals Inc. reported the results of theclinical phase II trial showing that 66% of the patients with ovarian cancer experiencedmeaningful disease stabilization and limited side effects.

Polyamino acids grafted with drugs on the side chains are another class ofpolymer–drug conjugates that have demonstrated high drug loading and efficacyIn the case of polyglutamate-glycine-campthotecin(CT-2106), degradable linkers have allowed drug loadings ranging from 5% to50%. Using a glycine linker, drug loadings were increased threefold over polyglutamate-campthotecin alone due to reduced steric hindrance. However, a formulationwith a drug load of ~30% was selected for clinical trials due to superiorstability and efficacy in human tumor xenograft mice models. Meanwhile, Xyotax, a similar polymer–drug conjugate (polyglutamate-paclitaxel),is in 22 clinical trials at the moment for multiple cancer therapies including prostatecancer, metastatic breast cancer, neck cancer, metastatic colorectal cancer, andrecurrent NSCL (Phase III). Paclitaxel is grafted to polyglutamic acid (30–40 kDa)to reach a drug load of 20–40% by weight. Theclinical data shows an improvement in median survival in Xyotax patients comparedwith the control group, although there were no differences in the overallsurvival. One benefit of the treatment was the reduction of multiple side effectsincluding neurotoxicity. Overall, polymer–drug conjugates areconsidered simple nanocarrier systems, but tuning the optimal formulation mightrequire extensive development. For example, small changes in the polymer–drugconjugation efficiency may significantly modify the pharmacokinetic parametersand tissue biodistribution.

3. Polymeric Nanoparticles

Polymeric nanoparticles may represent the most effective nanocarriers for prolongeddrug delivery. The early in vitro and in vivo development of polymericnanoparticles loaded with drugs in the 1980s using polyalkylcyanoacrylate-basednanoparticles releasing doxorubicin led to multiple reportsusing polymer-based materials for drug delivery. Langer and Folkman demonstrated the first controlled release of macromolecules usingpolymers, which allowed the development of anti-angiogenic drug delivery systemsfor cancer therapy and opened new areas for the delivery of macromolecules.In 1994, Langer et al. described nanoparticles composed of poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) and PEG block copolymer as “long-circulatingnanoparticles” due to their stealth properties, leading to an interest in polymeric nanoparticles and their therapeutic applications. Only a fewpapers per

year were published using polymeric nanoparticles as a drug deliverysystem in the 1990s in contrast to ~200 papers in 2008 Polymeric nanoparticles provide significant flexibility in design because polymerscan be biodegradable or nonbiodegradable, and can be made synthetically orderived from natural sources. Some common polymers used for nanoparticleformation include poly(lactic acid) (PLA), dextran, and chitosan. Biodegradablepolymers are typically degraded into individual monomers, which are metabolizedand removed from the body via normal metabolic pathways. Degradation and drugrelease kinetics can be precisely controlled by the physicochemical properties of thepolymer, such as molecular weight, dispersity index, hydrophobicity, and crystallinity.In general, drugs can be released in a controlled manner with first-orderkinetics due to drug diffusion through the polymeric matrix or triggered in responseto the local environment. The nanoparticle surface is usually sterically stabilized bygrafting, conjugating, or adsorbing hydrophilic polymers such as PEG to its surface,which can also reduce hepatic uptake and improve circulation half-life.

4. Micelle Nanoparticles

Micelles are composed of lipids or other amphiphilic molecules, such as polymersor polyamino acids, and self-assemble into small nanoparticles composed of a hydrophobic core. Micelles have been developed as drug delivery carriers forhydrophobic drugs; There are multiple examples of micellar formulations under investigationor in clinical trials, such as Genexol-PM;, NC-6004, NK105, and the NK91. Genexol-PM is the first nontargetedpolymeric micellar formulation approved for cancer therapy. It wasapproved in Korea in 2006 as a first-line therapy for metastatic breast and NSCLcancer (currently in Phase III). It is currently being evaluated in a clinical phase I. trial in the USA for metastatic pancreatic cancer therapy. Genexol-PM is composedof a block copolymer PDLLA (1.75 kDa)–mPEG (2 kDa) forming micelles with asize of ~60 nm and paclitaxel loading of ~15% (w/w). The maximum tolerated dose(MTD) of Genexol-PM is threefold higher than Taxol (60 mg kg_1 vs. 20 mg kg_1, respectively) and the median lethal tolerated dose (LD50) using Sprague–Dawleyrats was reported to be ~20 times higher than Taxol. Interestingly, the area under theplasma concentration (AUC) was similar for both formulations. However, paclitaxelhad more significant accumulation in tissues such as the liver and tumor withthe Genexol-PM formulation, leading to differential tumor cytotoxicity and reductionof tumor volume. Results of a clinical phase I trial showedthat while the MTD was almost double (390 mg m_2) for Genexol-PM compared toTaxol with similar toxicological profiles, the

recommended dose was determined tobe 300 mg m_2. The clinical phase II trial in Korea evaluatedGenexol-PM as a co-therapy with cisplatin for advanced NSCL in contrast to asingle agent therapy. The clinical phase II results showed ~30%of the patients had stable disease status and 60% of the patients had an increasedsurvival of one year using slightly lower doses of cisplatin than with the combinedtreatment of Taxol with cisplatin (60 mg m_2 versus 75 mg m_2, respectively)Other companies such as Labopharm and Intezym are alsodeveloping micelle systems for the delivery of a myriad of anticancer agents usingformulations with sizes ranging from 10 to 200 nm using polyamino acids.

5. Dendrimer Nanoparticles

Dendrimers are globular macromolecules (5–10 nm) with well-defined branchingarchitectures and surface functional groups available for further modification. Themultifunctional capabilities possible through controlled synthesis methods areleading to new classes of dendrimers that can carry drug molecules, diagnosticagents, and targeting molecules. Dendrimers have remarkable molecular monodispersityand suitable pharmacokinetic properties for systemic drug delivery withcleavable chemistry for drug dissociation. Amphiphilicdendrimersare able to form micelles by self-assembly with hydrophilic groups on thesurface for functionalization. Drug release kinetics are controlled through theproperties of the polymer chains, which can be designed to be degraded for releaseof a payload.Baker et al. have developed “avidimers”, which are dendrimers targeted to tumor vasculature using a methotrexatepolyamidoamine(PAMAM) bioconjugate platform functionalized with smalltargeting ligands. Non-targeted and folate-targeted G5-PAMAM dendrimers differentially accumulated into a human KB cell line xenografttumor model within a day (8%–10% targeted versus 2% non-targeted I.D./g oftissues). Higher accumulation in the tumor resultedin the inhibition of tumor growth, lower toxicity, and longer survival time comparedto free drug at equal dosage. More importantly, recent efficacy studies usingtargeted transferrin-cyclodextrin-siRNA nanoparticles (CALAA-01, ~70 nm) inanimal models of human epithelial cancer showed tumor size reduction and differentialdistribution in tumors. The preclinical data motivated further development of CALAA-01. Thetoxicological results reported in April 2007 for CALAA-01, which was the firsttargeted, polymeric nanoparticle platform in non-human primates, led to the submission of an investigational new drug application and humanclinical trials for solid tumor therapy in May 2008.

6. Polymersome Nanoparticles

Polymersomes have a structure similar to liposomes, but are composed of syntheticpolymer/polypeptide amphiphiles and self-assemble to form polymer shell vesicles(~100 nm) when hydrated and extruded. Discher et al describedvesicles made of amphiphilicdiblock copolymers with low water permeability. The hydrophilicity/hydrophobicity ratio is used to control the morphology of the nanoparticle,which can range from spherical to cylindrical. The membrane core thicknesscan be controlled by the molecular weight of the diblock copolymer.Polymersomes show higher stability and lateral fluidity than liposomes and therelease is triggered by the degradation of the polymer chain and destabilization ofthe shell layer. Incubation of polymersomes in the blood showed adherence anduptake by white blood cells within 10 h. In vivo results using a breast cancer tumorxenograft model showed therapeutic efficacy after a single i.v. injection using.polymersomes loaded with paclitaxel and doxorubicin at the maximum tolerateddose (2.5 mg kg_1 for each drug).

7. Protein Nanoparticles

Protein-based drug delivery systems have recently made a big impact with albuminbounddrug nanoparticles (~130 nm). The recent approval of albumin-boundpaclitaxel by the Food and Drug Administration(FDA) for metastatic breast cancer therapy, as well as multiple clinical trialscurrently in progress for other types of cancer, has now opened the possibility ofusing protein-based nanoparticles for delivery of therapeutic agents. Given the limiting pharmacokinetic properties and numerous side effectsof Taxol (hypersensitivity), the albumin-bound paclitaxel allows the formulation ofthe hydrophobic drug in a solvent-free solution. Albumin is a natural noncovalent physiological transporter of molecules across endothelial barriers through.transcytosis-mediated mechanism (caveolae vesicle). Preclinical studies haveshown that the concentration of paclitaxel bound to albumin in endothelial cellsand in the extravascular space was significantly increased (3–10 fold). Data suggests that albumin may have intrinsic targetingabilities to tumors, although the enhanced permeability and retention (EPR) effectmay play an additional role in tumor accumulation. Overall, the albumin-boundpaclitaxel formulation allowed higher dosages than the Taxol formulation(260 mg m_2 vs. 175 mg m_2, respectively) and demonstrated improved efficacyand safety. Abraxane is currently being tested as a first-linetherapy or in combination with other drugs (rapamycin, verinostat, etc.) for metastaticbreast cancer and other cancers that have been shown to be sensitive to taxanedrugs, such as ovarian and prostate. In addition, albumin is

now being tested as aplatform for delivery of other molecules that have reduced water solubility, such asrapamycin (~2.5 mg ml–1). Albumin-bound rapamycin (ABI-009) has been in aclinical phase trial for the treatment.

8. Biological Nanoparticles

Biological nanoparticles such as bacteria are unicellular microorganisms withdifferent shapes and sizes that encapsulate essential components of the cytoplasmas well as hydrophobic and hydrophilic molecules. One example of biologicalnanoparticles being evaluated for cancer therapy is a drug delivery system developedby EnGeneIC Pty Ltd called a "nanocell", which consists of anucleateglobular bacteria (~400 nm). The absence of DNA prevents endogenous mutationsand replication originally reported in 1967. It has been demonstratedthat a nanocell can be efficiently loaded with molecules of different solubilityand charge, such as doxorubicin, paclitaxel, and siRNA, through drug diffusioninto the bacteria within a few hours. No signs of toxicityhave been reported in large animals such as pigs and monkeys with repeateddosages at high titers, although there is the potential.

9. Inorganic Nanoparticles

Inorganic nanoparticles are primarily metal-based and have the potential to besynthesized with near monodispersity. Inorganic materials have been extensivelystudied for imaging using magnetic resonance and high-resolution superconductingquantum interference devices while their intrinsic properties have been explored fortherapy. Several types of metal nanoparticles are able to convert energy into heat at levels up to 70_Cthrough near-infrared light excitation or oscillating magnetic field stimulation. Iron oxide nanoparticles coated with aminosilane (Nanotherm M01) are in clinical phase II trials in Germany for brain cancer therapyand recurrent prostate cancer therapy using hyperthermia as well as thermoablationmethods. The phase I results showed that prostate tumor cells can be locally killedby magnetic iron oxide nanoparticles.

Nanoparticles wereinjected locally using ultrasound to guide tumor injections and patients were treatedonce a week for 1 h over two months. The small nanoparticles (~20 nm) are ableto penetrate tumors, enter cancer cells, and generate heat under magnetic fields(50 and 100 kHz), allowing treatment width between 20 and 30 cm and within acircular area of 20 cm of diameter. The authors report no dose-limiting toxicitiesand mild discomfort from internal heating. Similarly, silica nanoparticles coated with gold that absorb near-infrared laser energy and covert it into heat to kill solidtumors are currently under investigation in a pilot study for

head and neck cancertherapy. In vivo results of nanoshell-mediated NIR (nearinfrared) thermal therapy using human breast cancer xenograft models showedthat the nanoparticles induced irreversible cancer tissue damage at a temperature~40_C. However, the temperature variance between different mice treated wasquite significant (28–60_C) and was suggested to be due to differential distributionof nanoshells in the treated volume of the tumor. In addition, the maximumrecorded temperature was only ~1 mm under the skin. Recently, the same nanoparticles(150 nm) were used for brain cancer treatment in an orthotopic caninemodel.

Tumors were killed using percutaneous infiltratedNIR fibers reaching a temperature of ~70_C in tumor tissues and ~50_C in normalwhite and grey matter, which is expected to significantly damage non-diseasedareas of the brain.Surface properties and functionalities of gold nanoparticles have also been usedfor the delivery of surface-bound therapeutics. Aurimune (CYT-6091) is anexample of tumor necrosis factor (TNF)-alpha bound to PEG-coated gold nanoparticles(~27 nm) developed by CytImmune Sciences, Inc. for solid tumortherapy. TNF-alpha is a potent cytokine with antitumorcytotoxicity which requires incorporation into a nanocarrier formulation to reducesystemic toxicity. The results show that nanoparticle formulations delayed thetumor growth with local heating (42_C for 1 h) using a SCK mammary tumorxenograft mouse model. However, the combined treatment showed a higherefficacy and suppression of intratumor blood flow.

PreliminarySEM micrographs of nanoparticles accumulated in breast tumor tissue sectionsin contrast to healthy tissues showed possible targeting of the nanoparticlesby the EPR effect. Many other formulations are still in the discovery stage usingcombinations of drugs such as TNF with paclitaxel, doxorubicin or interleukin-12.However, the load of therapeutic agent is reported to be several hundreds ofmolecules due to the surface adsorption density, which may limit the effect ofthe therapeutic agent. Recently, Adair's group has reported the encapsulation of organic molecules in calcium phosphatenanocomposite particles (~27 nm) for intracellular imaging and delivery. Calciumphosphate-based nanoparticles are biocompatible and their pH dissolution propertiescan be used for controlled release of molecules in the acidic tumor environment.In vitro studies show high uptake of the nanoparticles in bovine aorticendothelial cells and the delivery of hexanoyl-ceramide (Cer-6) to human vascularsmooth muscle cells showed 100% inhibition of cell growth at 200 nM of drug.

This technology is now being developed by Keystone Nanofor imaging and delivery of therapeutic agents.Non-specific accumulation into healthy tissues is always a concern for nanoparticledrug delivery systems. Using local sensitization through light or temperaturemay reduce overall toxicity, but it is expected to damage adjacent healthy tissues aswell. Ultimately, inorganic particles may not provide advantages over other typesof nanoparticles for systemic targeting of cancer cells because they are not biodegradable.

10. Hybrid Nanoparticles

Hybrid nanoparticles are recently developed nanocarriers that combine advantagesfrom existing systems with well-characterized properties to form lipid–polymernanoparticles and solid liposomal nanoparticles. Hybrid nanoparticles are composedof at least two different materials to form the core and the corona structure. In general, metallic and polymeric materials form the core and are coated with asingle or multiple lipid layers to form a protecting membrane (corona) similar to aliposome or micelle. We and others have developedhybrid nanoparticles for cancer therapy. Sasisekharan and co-workers have reported PLGA-core nanoparticles coated with a bi-phospholipidlayer to carry multiple drugs for cancer therapy using melanoma and Lewis lungcarcinoma models. In their system, doxorubicin is conjugated to PLGA to formthe core of the nanoparticle (~1% load by weight of doxorubicin, 70% encapsulationefficiency) while an anti-angiogenesis drug, combrestatin, is mixed withphospholipids and encapsulated in the lipid bi-layer during the self-assemblyprocess to form nanoparticles (~200 nm) described as “nanocells”. The drugswere release at different rates over a period of ~3 days, with combrestatin releasedfirst to reduce vascular density in the tumor followed by the release of doxorubicinto kill the cancer cells. The results showed a significant delay in tumor growth andincreased survival time in both cancer models, suggesting accumulation of thenanocell by the EPR effect and added therapeutic value by delivering multipledrugs.

The nanocell technology is now in preclinical development by CeruleanPharma.Others have reported solid-lipid nanoparticles using different polymers andformulations in vitro and in vivo for combination therapy. Recently, Thevenotet al.described a mechanism for the encapsulation of a hydrophobic polymer core (PLA) in PEG-liposomes. As part of the work, the importance of PEGchain length to sterically stabilize lipoparticles with optimal colloidal stability wasdemonstrated (PEG (5 kDa) at 10% of lipid content). Our group has reported a

one-step formulation for self-assembly of a singlelayer of lipid on the hydrophobic surface of PLA nanoparticles (size <100 nm).

Surface functionalization using different lipid constituents allows the precise controlof the charge and targeting ligand density, leading to stable hybrid nanoparticleformulations. In addition, drug loading was significantlyincreased up to ~8% by weight and the release kinetics of docetaxel was shownto be controlled by the lipid layer on the surface of the nanoparticles. Multifunctionalnanoparticle technologies are now able to combine multiple therapeutic approaches that approaches such as photothermal and drug delivery, and simultaneous delivery of therapeutic drugsand imaging agents.

Startisticesfor Cancer Therapy Using Nanoparticles[5,6,7]

1. Metastatic Cancer

Metastatic cancer is a clinical description for the spread of cancer cells from theprimary tumor site to distant organs, establishing secondary tumor sites. Detachment of cancer cells from the primary tumor site and circulation in the blood allowsthe cells to arrest in organs such as the lungs, liver, lymph nodes, skin, kidneys, brain, colon, and bones, where they can extravasate and proliferate. Despite significant increases in the understanding of metastaticcancer pathogenesis, early diagnosis, surgical methods, and irradiation treatment, most cancer deaths are due to metastases that are not curable. Reasons for thisinclude resistance to treatments, difficulty accessing the tumor sites and removingall cancer cells during surgery, or physiological barriers for drug access such as theblood–brain barrier (BBB). Therefore, improving therapy of metastatic cancer isstill a challenge even though multiple therapeutic approaches are approved or in clinical development. An improved understanding of cancer biology, including microenvironmentfunctions, signaling pathways, and metastasis evolution, has resulted in clearadvances in cancer therapy. Drugs have now been developed against a range of targets including matrix metalloproteinase inhibitors, epidermal growth-factorreceptor inhibitors, transferase inhibitors, migration inhibitors, and angiogenesisinhibitors. However, due the complexity of tumor progression, tumor compositionblood vessel structures, and drug resistance mechanisms, most of the currenttherapies have provided limited extension of survival time across multiple cancertypes with the exception of imatinib (tyrosine kinase inhibitor) for gastrointestinalstromal tumor.

Knowledge of drug action pathways andcellular drug resistance mechanisms to specific drugs has allowed the developmentand evaluation of promising drug combinations. Trials of

combinations of agents are usually designed to enhance the activityof the primary agent or to inhibit different pathways to circumvent drug resistanceto the primary agent. The critical advantage of using drug combinations is toprevent drug resistance development during cancer therapy without increasing theknown side effects of each drug. Although it is believed that tumor growth andmetastases are adaptable mechanisms, higher doses of single drugs are able toprevent resistance mechanisms in vitro in some cases. However,multi-drug regimens with synergistic combinations have been shown to be moresuccessful in patients, probably due to cell heterogeneity in tumors and betweenpatients. Unfortunately, multi-drug treatment requires complicated dosing regimens.Nanoparticle delivery systems offer solutions to both of these approaches.Delivery of single drugs in nanoparticles results in increased drug concentrations inthe tumor, allowing higher doses compared with free drug using both non-targetedand targeted delivery. Nanoparticles can also be engineered to carry multiple drugsthat are delivered together in one particle with control over the release rate of eachdrug, preventing the need for complicated multi-drug dosing regimens and improvingpatient compliance.

2. Non-Targeted Nanoparticles

Non-targeted nanoparticles circulating in the blood have been shown to significantlyimprove drug bioavailability and accumulation in tumors through theenhanced permeability and retention effect (EPR). The EPR effect allowsthe passive targeting of nanoparticles to tumors due to pathological abnormalitiesin the tumor vasculature. Interendothelial gapdefects increase vascular permeability in tumors, allowing extravasation of nanoparticlesup to 400 nm. Accumulation of nanoparticles is further enhanced due to poor lymphatic drainage in tumors. The local release ofanti-cancer drugs from nanocarriers in the extravascular space results in anincreased intra-tumoral drug concentration. In general, hydrophobic drugs releasedextracellularly will diffuse and be taken up by cancer cells, leading to enhancedtumor cytotoxicity. Since cancer cell populations, cell density, antigen expression, microenvironment, and vasculature density are significantly different across differentcancers and even within primary and secondary metastatic sites, nanoparticlebiodistribution and circulation time represent critical parameters for cancertherapy.

Multiple factors affect the pharmacokinetic behavior of nanoparticles, butthe surface charge, size, nanoparticle shape and stealth properties are among themost critical. As described in thenanoparticle technologies section above, five common types of nanoparticles areapproved

or in late stage of clinical trials, including polymer–drug conjugates,micelles, protein-based carrier, liposomes, and polymeric nanoparticles. Overall,non-targeted nanoparticles accumulate in tumor xenograft mice models in therange of 1–4% of I.D./g of tissue, although these numbers are difficult to comparedue to different post-injection time assessments. Polymer–drug conjugates are the smallest (1–20 nm) and have acirculation half-life in human ranging from hours to days depending on the system.To ourknowledge, dextran–camptothecin (DE-310) has the longest circulationhalf-life (~300 h) in humans and has been shown to have no major toxicity compared to the free drug formulation in clinical phase II trials. However, its therapeutic efficacy might be limited by its dosageregimen compared to PEG–camptothecin and polyglutamate–camptothecin conjugate. (7,000 and 25 mg m_2, respectively).

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argininedeaminase (Hepacid, 7 days) and PEG–camptothecin (Prothecan, 40 h). In general, larger nanoparticles such as micellesand liposomes seem to have a shorter circulation half-life in the blood (2–50 h) buthigher maximum tolerated doses. The Genexol-PM formulation of paclitaxel isgiven at a twofold higher dosage than HPMA–paclitaxel (PNU166945) and polyglutamate - paclitaxel (Xyotax). However, it is not clear whether circulation halflifeor maximum tolerated dose is the most critical for optimum accumulation intumor tissues. For example, polycyclodextrin–camptothecin micelles (IT-101) andPEG–camptothecin conjugates show similar circulation half-life but significantlydifferent accumulation of drug in tumor xenograft models. However, this may bedue to the different xenograft models used. Unfortunately, it is difficult to comparethe therapeutic efficacy of different systems in humans due to different patient populations and disease stages.

Clinical data suggests that the circulation half-lifeand biodistribution of nanoparticles are related to the physicochemical propertiesof the vehicle. This is consistent with the in vivo biodistribution and circulationhalf-life results using animal models. In addition, it is wellestablished that hydrophilic polymers such as PEG can be grafted, conjugated, orabsorbed onto the surface of nanoparticles to form a corona, which provides stericstabilization and confers “stealth” properties by reducing protein absorption andrapid clearance.Recently, we and others; investigated nanoparticlesurface properties and adsorption of proteins present in the blood. Lindman et al.found that protein adsorption kinetics and compositiondepends on particle size and surface hydrophobicity. The results show thatalbumin adsorbed more on the surface of 200 nm nanoparticles than on smallernanoparticles (70 nm). Nanoparticles with hydrophilic surfaces significantlyprevented protein adsorption. It was suggested that smaller nanoparticles (70nm) have higher curvature which reduce protein adsorption of larger proteins.Interestingly, the results show a binding competition leading to adsorptionexchanges between proteins despite different concentrations and affinities.Lundqvist et al. have shown that protein adsorption depends significantly on the size and charge of the nanoparticles. Identificationof protein compositions bound to the nanoparticles showed a mixture of proteinswith different functions such as immunoglobulin, lipoproteins, complementpathways proteins, and coagulation factor proteins. Similarly, our group investigatedcomplement activation, blood clotting, and protein adsorption properties of hybrid nanoparticles with precise control of the charge. DeSimone’s group has investigated internalization pathways and in-vivo biodistribution of polymeric nanoparticles with different sizeand shapes. Nanoparticles were more efficiently taken up byHela cells than

microparticles. Rod-like nanoparticles were internalizedefficiently than their spherical counterpart in vitro but there was no clear evidenceof the effect of shape affecting the biodistribution and circulation half-life of thenanoparticles in vivo. Other groups have also shown differential uptake of nanoparticleswith different shapes. These findings are highlighted by the mechanical modeling reportedby Decuzzi showing thatnanoparticle geometry and physicochemical properties contribute to the cellularinternalization rate and adhesion forces on the surface of the cells. Mathematicalmodels suggest that nanoparticle size will control its interaction with cells, especiallythe endothelial wall of vasculatures through a margination dynamic mechanism. Finally, the surface structure of the nanoparticlecan affect its cellular uptake.Recent studies have shown that nanoparticles coatedwith sub-nanometer striations demonstrate enhanced uptake compared with random.

3. Targeted Nanoparticles

The concept of targeted therapy appeared in the late 1970s with the development ofantibodies whereas the application of targeted nanoparticlesappeared later using immunoliposomes. Advances in cancer proteomics and bioinformatics have allowed the developmentof targeted therapies, which were referred to as a “magic bullet” by the visionaryPaulEhrlich. Nanocarriers may be surface functionalizedwith biomolecules for “active” tumor targeting. Surface ligands includeantibodies, aptamers, peptides, or small molecules which recognize tumor-specificor tumor-associated antigens in the tumor microenvironment. The active targeting mechanism takes advantage ofhighly specific interactions between the targeting ligand and certain tissues or cellsurface antigens to increase cellular uptake and increase tumor retention. Conjugationapproaches have been developed to control the amount of targeting ligands onthe surface of the nanoparticles. In the case of weak binding ligands, multivalentfunctionalization on the surface of the nanoparticles provides sufficient avidity. Ingeneral, small molecule ligands such as peptides, sugars, and small molecules aremore attractive than antibodies due to higher stability, higher purity, ease ofproduction through synthetic routes, and non-immunogenicity.

There are two common approaches for receptor-mediated targeting. This firstapproach is to target the tumor microenvironment, including the extracellularmatrix or surface receptors on tumor blood vessel endothelial cells,which is usually most efficient for the delivery of immune induction or antiangiogenesismolecules. The second approach is to target tumor cell surfacereceptors for intracellular delivery of cytotoxic agents or signal-pathwayinhibitors.

Nanocarriers targeted to the extracellular portion of transmembranetumor antigens are generally specifically taken up by cancer cells through receptor-mediated endocytosis for efficient delivery of therapeutic loads intracellularly.

Although it is not clear which approach will provide the highest therapeuticefficacy for treatment of cancer metastases, a recent report using integrin receptortargeted nanoparticles delivering a cytotoxic drug (doxorubicin) showedpromising data in primary and metastatic sites of human renal and pancreaticcarcinoma mouse xenograft models. Targeted nanoparticlesshowed tumor accumulation and decreased the tumor weight in the primary tumorand hepatic lymph node metastasis. We and others have developed targeted nanoparticles for multiple cancer types.

Ourgroup has developed nucleic acid aptamer functionalized nanoparticles for controlleddrug delivery. Aptamers are able to bind to specific targets with highaffinity and specificity, resulting in clinical development for multiple applications. We are developing multiple technologies using targeted nanoparticle–aptamerbioconjugates for drug delivery to prostate cancer. In a proof-of-concept study, polymeric nanoparticles utilizing aptamers as the targeting ligand showedalmost complete reduction in tumor growth in a human prostate cancer tumorxenograft mice model. All the treated micesurvived more than three months in contrast to other controls. Subsequently, wereported a novel strategy for formulating targeted nanoparticles that was testedin vivo. We also engineered hydrophilic cisplatin drugs for efficient encapsulation into PLGA–PEG nanoparticles.

PlasmonicPhototharmal Therapy Using Gold Nanoparticals[8,9]

The use of heat has become one of the major methodsfor tumor therapy since its ancient usage in 1700 BCwhen a glowing tip of a firedrill was used for breast cancertherapy. Later heating sources ranging from radiofrequencyto microwaves as well as ultrasoundwaves were introduced to induce moderate heatingin a specific target region, which is termed as hyperthermia.Hyperthermia is commonly defined as heating tissue to atemperature in the range 41–47°C for tens of minutes. Tumors are selectively destroyed in this temperature rangebecause of their reduced heat tolerance compared to normaltissue, which is due to their poor blood supply. Hyperthermiacauses irreversible cell damage by loosening cellmembranes and denaturing proteins. But the applications ofthe heating sources conventionally employed for hyperther-mia are limited because of their damage to surroundinghealthy tissues.

A revolution in cancer therapy has taken place by theemerging use of laser light to achieve controlled andconfined thermal damage in the tumor tissue. Laser, theacronym for light amplification by the stimulated emissionof radiation, is an optical source that emits photons in acoherent and narrow beam. It was proposed in 1959 and first demonstrated in 1960. Laser usage in surgerywas first reported by ophthalmologists in 1963 andthen reported for tumor eradication in 1965 followedby wide interest in late 1960s. The laser light,usually neodymium–yttrium aluminum garnet (Nd–YAG, 1.06 um) and CO2 laser (10.6 um) can either betransmitted from optical fiber tip to exposed tumors in theair or delivered into a confined space by inserting the bareend of the fiber into the center of the target tumor, which isoften called interstitial laser hyperthermia. Laserlight has the characteristics of monochromaticity, coherence, and collimation. These properties provide anarrow beam of high intensity, which transmits deep downinto the target tissue with minimal power loss and greatprecision.

The biggest disadvantage of laser therapy is its nonselectivity. Both normal and tumor cells in the path ofthe laser light are damaged. The requirement of the highpower density is another problem. High power laser outputup to tens to hundreds of watts has to be used to efficientlyinduce the tumor oblation.Another type of tumor therapy method is the photodynamictherapy (PDT), also known as photochemotherapy, which involves cell destruction caused by means of toxic singlet oxygen and/or other free radicals that areproduced from a sequence of photochemical and photobiologicalprocesses. These processes are initiated by thereaction of a photosensitizer with tissue oxygen uponexposure to a specific wavelength of light in the visible ornear-infrared (NIR) region. The earliest sensitizer used wasacridine, which was reported in 1900 to kill paramecia and followed by eosin for skin cancer treatment in 1903.

Although many chemicals have been later reported forphotochemical therapy, porphyrin-based sensitizers lead the role in clinical applications because of theirpreferential retention in cancer tissues and due to the highquantum yields of singlet oxygen produced. The Photofrin, which is a purified hematoporphyrin derivative, has been approved for clinic trials by the US Food and DrugAdministration. Porphyrin-based therapy can only be usedfor tumors on or just under the skin or on the lining ofinternal organs or cavities because it absorbs light shorterthan 640 nm in wavelength. For deep-seated tumors,second generation sensitizers, which have absorbance inthe NIR region, such as core-modified porphyrins, chlorins

phthalocyanine, and naphthalocyanine have been introduced. A major drawback of PDT isthat the photosensitizing drug stays in the body for a longtime, rendering the patient to be highly sensitive to light.

An alternative to PDT is the photothermal therapy (PTT) in which photothermal agents are employed toachieve the selective heating of the local environment. When the PTT agents absorbs light, electronsmake transitions from the ground state to the excited state.The electronic excitation energy subsequently relaxesthrough nonradiative decay channels. This results in theincrease in the kinetic energy leading to the overheating ofthe local environment around the light absorbing species.The heat produced can be employed for local cell or tissuedestruction. The photoabsorbing agents can benatural chromophores in the tissue or externallyadded dye molecules such as indocyanine green, naphthalocyanines, and porphyrins coordinated withtransition metals. Natural chromophores, however, suffer from very low absorption. The choice of theexogenous photothermal agents is made on the basis oftheir strong absorption cross sections and highly efficientlight-to-heat conversion.

This greatly reduces the amount oflaser energy required to achieve the local damage of thediseased cells, rendering the therapy method less invasive.But the problem with dye molecules is their photobleachingunder laser irradiation.In recent years, the tremendous development of nanotechnologyhas provided a variety of nanostructures withunique optical properties that are useful in biology andbiomedicinal applications. From the point of theview of cancer therapeutics, noble metal nanoparticlesbecome very useful as agents for PTT on account of theirenhanced absorption cross sections, which are four to fiveorders of magnitude larger than those offered by conventionalphotoabsorbing dyes. This strong absorption ensureseffective laser therapy at relatively lower energies renderingthe therapy method minimally invasive. Additionally, metalnanostructures have higher photostability, and they do not suffer from photobleaching. Currently, gold nanospheres, gold nanorods, gold nanoshells, gold nanocages, and carbon nanotubes arethe chief nanostructures that have been demonstrated inphotothermal therapeutics due to their strongly enhancedabsorption in the visible and NIR regions on account oftheir surface plasmon resonance (SPR) oscillations. Ofthese structures, the first three nanostructures are especially promising because of their ease of preparation,ready multi-functionalization, and tunable opticalproperties. In the present review, we discuss the photothermalproperties of these plasmonic nanostructures andtheir

application in selective PTT. We propose the name plasmonicphotothermal therapy (PPTT) for this treatmentto distinguish it from PTT and PDT.

Photothermal properties of plasmonic goldnanoparticles[10,11,12]

In 1857, Faraday made colloidal gold for the firsttime by reducing gold chloride with phosphors andrecognized that the reddish color was due to the small sizeof the colloidal gold particles. In 1951, Turkevich et al.simplified the method by using sodium citrate asreducing agents. Since then, the interaction between lightand gold nanoparticles has been widely studied. Gold nanoparticles absorb light strongly in the visibleregion due to the coherent oscillations of the metalconduction band electrons in strong resonance with visiblefrequencies of light. This phenomenon is known as the SPR. The SPR frequency is dependent on the type ofthe metal, the size and shape of the metal nanoparticles, aswell as the dielectric constant of the surrounding medium,thus imparting a unique optical tunability to the nanostructures.When the size increases, the surface plasmon absorptionmaximum slightly redshifts.

When thenanoparticles form assemblies or aggregates, the surfaceplasmon absorption maximum redshifts to the NIR region.Interestingly, when the shape of the gold nanoparticles ischanged from sphere to rod, the SPR spectrum splits intotwo bands: a stronger long-wavelength band in the NIRregion due to the longitudinal oscillation of electrons and aweaker short-wavelength band in the visible region around 520 nm due to the transverse electronic oscillation. Unlike spherical nanoparticles, theabsorption spectrum of the gold nanorods is very sensitiveto the aspectratio(length/width). With an increase in thenanorod aspect ratio, the SPR absorption wavelengthmaximum of the longitudinal band significantly redshifts. Similarly, when the solid gold nanospheres ar changed to gold shell structures, the absorption maximum also greatly redshifts. In 1998, Halas and coworkers at RiceUniversity developed the gold nanoshell structure,which is composed of a silica core (100–200 nm in diameter) surrounded by a thin layer of gold shells (5–20 nm). Thenanoshells absorb and scatter strongly in the NIR region. The optical resonance of the nanoshells can be tunedby adjusting the ratio of the thickness of the gold shell tothe diameter of the silica core. It has been shownthat the smaller this ratio, the more redshifted is the SPRwavelength.

The photothermal properties of gold nanoparticles havebeen systematically studied using femtosecond transientabsorption spectroscopy by Link and El-Sayed, whohave shown that the photoexcitation of metal nanostructuresressults in the formation of a heated electron gas.

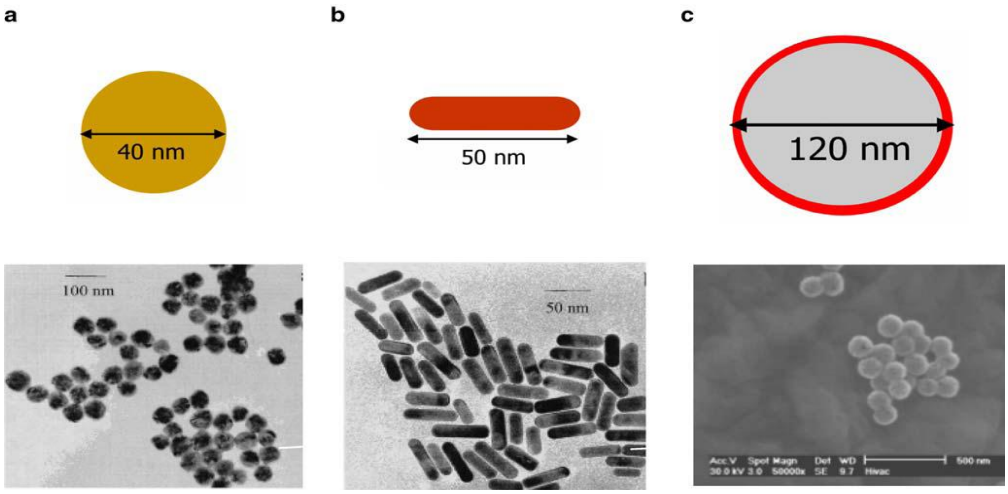

Fig. 3 Plasmonic gold nanostructures commonly used for PPTT.a.

Nanospheres (transmission electron microscopy [TEM] image reproducedwith permission from; b nanorods (TEM image reproduced with permission from c Nanoshells (TEM image reproduced with permission from.

Photothermal properties of plasmonic gold nanoparticles

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This highly efficient productionof heat energy from the absorbed light energy bygold nanoparticles make them greatly promising in thePPTT of cancers and other diseases. Further, in the case ofgold nanorods and gold nanoshells, this strong absorption canbe tuned to the NIR region a region where lightpenetration is optimal due to minimal absorption from tissuechromophores and water. This makes NIR-resonantgold nanostructures very useful for clinical therapy applicationsinvolving tumors located deep within bodily tissue.In addition to the local heating of the surroundingenvironment, which leads to irreversible cell destructionthrough protein denaturation and coagulation as well as cellmembrane destruction, bubble formation around goldnanoparticles is also involved in the case of short pulselaser

irradiation, which imposes mechanical stress leadingto cell damage. Irradiation with short laser pulses has beenshown to lead to the rapid heating of the particles and vaporizationof a thin layer of fluid surrounding each particle,producing a microscopic version of underwater explosionand cavitation bubble formation Zharov et al. also found that nanoclusters formed by theassembly of gold nanoparticles on human breast cancer cellssignificantly enhance the bubble formation causing moreefficient cancer cell killing.Very recently Khlebtsov et al. theoretically simulated thephotothermal conversion efficiency of the different nanostructuresincluding gold nanospheres, gold nanorods, goldnanoshells, linear chains, 2D arrays, and 3D clusters by calculating their SPR absorption spectra.

It was foundthat gold spheres with diameters of about 30–40 nm are most preferable, as their normalized absorption is maximalin the visible spectrum region. The nanorods with lengthbetween 15 and 70 nm were predicted to be most efficient.Of course, it would also be required that the longitudinalabsorption maximum be matched to the wavelength of theNIR laser to get optimal photothermal efficiency. Goldnanoshells with external diameters of about 50–100 nm andgold shell thicknesses of about 4–8 nm are estimated to bethe most effective due to the strong absorption and lowscattering near 800 nm.Bioconjugation and targetingMost laser-based therapeutic methods rely on the use ofendoscopes and fiber optic catheters to deliver lightspecifically to the tumor region.

Plasmonic gold nanostructures thus show great promise forthe selective PTT for cancer as well as other diseases. Wepropose the name PPTT for this treatment. It is realized thata number of variables need to be further addressed, e.g.,stability, biocompatibility, and chemical reactions of nanoparticlebioconjugates in physiological environments, bloodretention time, tumor extravasation, the fate of the nanoparticlesfollowing therapy, etc. We anticipate that thesuccess and promise of the initial use of plasmonicnanoparticles for selective PPTT could be efficientlyextended to clinical stage once the optimal parameters ofthese variables are identified, as is being done throughcurrent research studies.

Gold Nanoparticals And Synthesis[13,14,15]

Generally, gold nanoparticles are produced in a liquid ("liquid chemical methods") by reductionof chloroauric acid (H[AuCl4]), although more advanced and precise methods do exist. Afterdissolving H[AuCl4], the solution is rapidly stirred while a reducing agent is added. This causesAu3+ ions to be reduced to neutral gold atoms. As more and more of these gold atoms form, thesolution becomes supersaturated, and gold gradually starts to precipitate

in the form of subnanometerparticles. The rest of the gold atoms that form stick to the existing particles, and, if thesolution is stirred vigorously enough, the particles will be fairly uniform in size. To prevent theparticles from aggregating, some sort of stabilizing agent that sticks to the nanoparticle surface isusually added. They can be functionalized with various organic ligands to create organicinorganichybrids with advanced functionality.It can also be synthesised by laser ablation

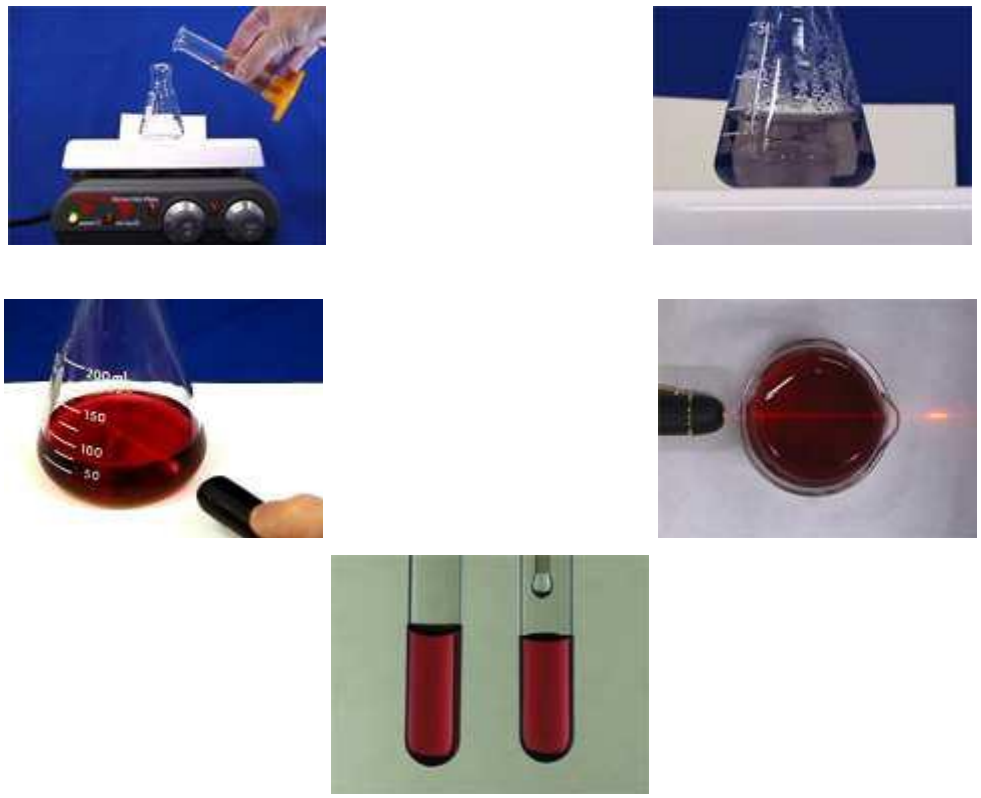

FIG. 4: Steps of Gold Nanoparticles Synthesis Shapes.

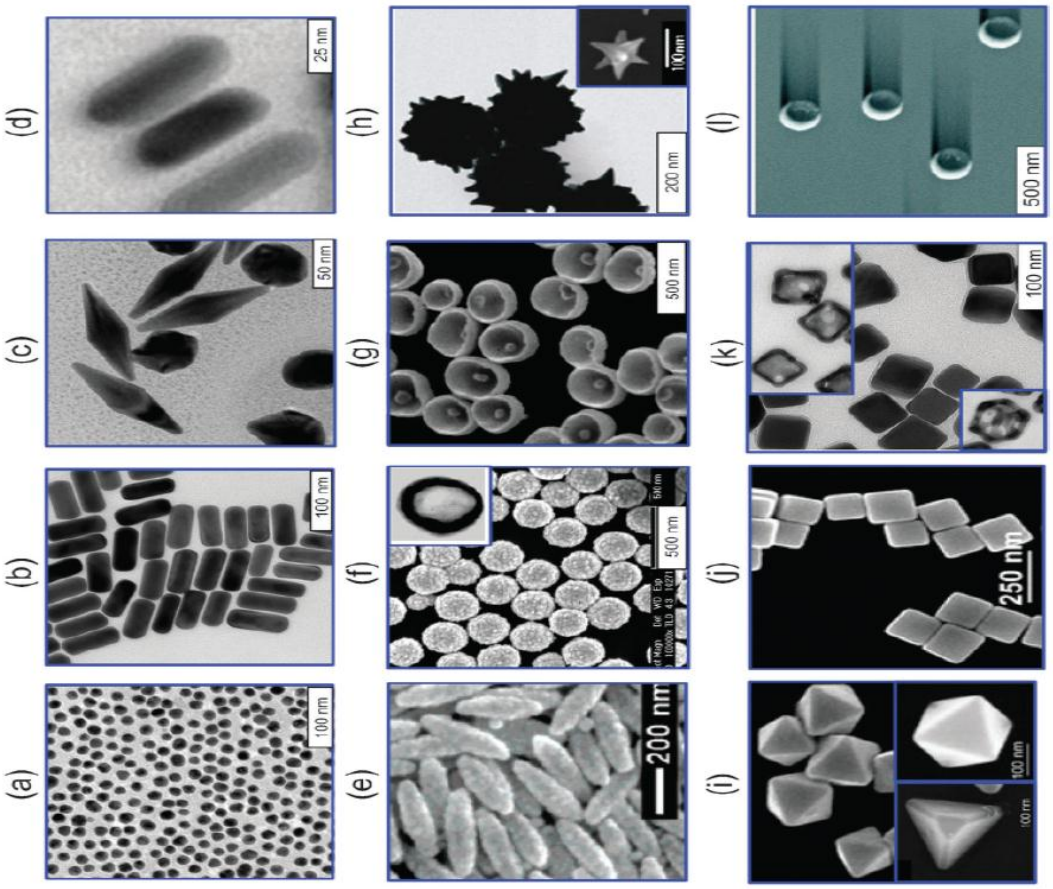

Figure 5: Various types of nano particals.

Synthesis of various gold nanoparticals[16,17]

Gold nanorods

In gold nanorods, electrons can oscillate in two independent directions (along the main axes andperpendicular to it): this generates two SPR absorption bands, the first one (perpendicular)being at the typical nanoparticles wavelengths and the second (longitudinal) in the NIR regionGold nanorods, which were developed during the sameperiod as gold–silica nanoshells, are generally smaller thannanoshells. Like gold–silica nanoparticles, gold nanorodsfluence threshold for gold nanorod conversion, photothermaltherapy would still be effective for tumors within 10 mm ofthe illuminated region. This correlates with the limitationsin vivo of NIR laser penetration

Gold nano shells

In 2003, Hirsch et al. were the fi rst to demonstrate photothermaltherapy using gold–silica nanoshells. Gold–silicananoshells, composed of silica cores with a thin overlay of gold,were the fi rst gold nanoparticles easily tunable to the NIR. Byvarying the size of the silica core and the thickness of the goldshell, the resonance of these nanoshells can span from the

visibleto the near infrared. Gold–silica nanoshell fabrication is basedon seed-mediated growth, where ‘seeds’ of gold colloid areattached to the silica cores, and additional gold is added for completionof the shell. Similarly to other gold nanoparticles, gold–silica nanoshells have been studied specifically for their potentialas imaging contrast agents with darkfield microscopy, twophotonmicroscopy, reflectance confocal microscopy, andoptical coherence tomography (OCT). In addition to havingutility in cancer imaging, nanoshells that are strong absorberscan induce cancer cell death by converting light into heatSilica-based gold nanoshells have been tested in vitroas targeted-therapy probes for human breast, prostate, brain, and liver cancers. In addition, nanoshells have demonstratedin-vivo therapeutic efficacy against xenografted subcutaneoustumors in mice and allografted tumors in dogs.

The larger size of gold–silica nanoshells as opposed to manyother gold nanostructures provides an advantage in scatterbasedimaging, but in-vivo delivery may be more challengingthan for smaller particles in some applications.

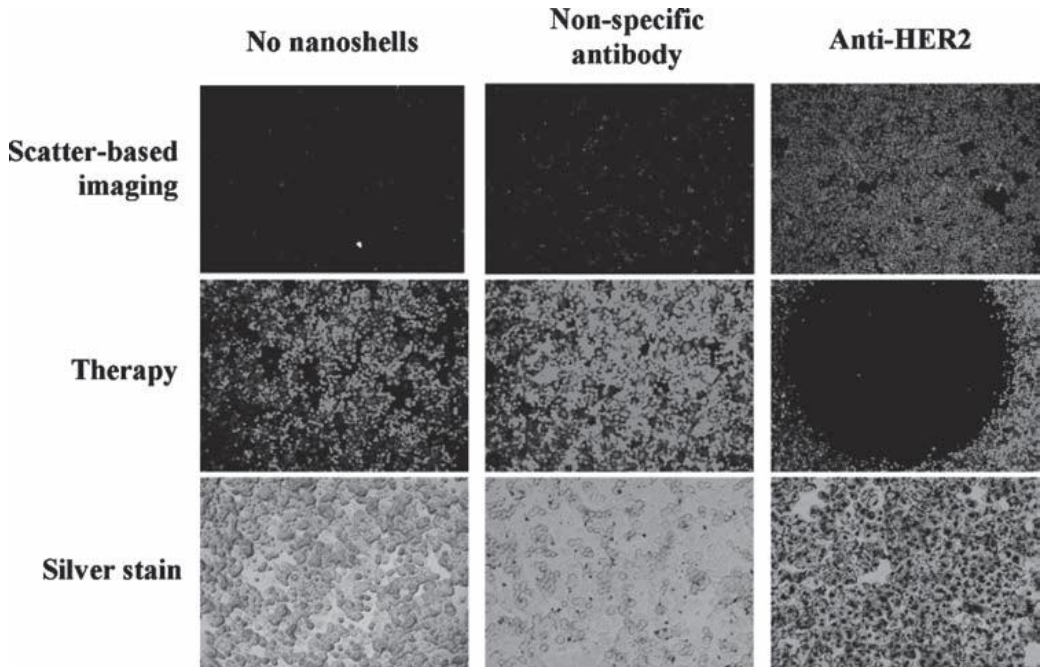

Figure 6. In-vitro imaging and therapy of human epidermal growth factor receptor 2 (HER2)-positive breast cancer cells using anti-HER2-conjugated gold–silica nanoshells. The top row is darkfield microscopy of each treatment group, the middle row is a live stain of the cells after irradiation withNIR light, and the bottom row is a silver stain to show nanoshell binding. The same nanoshells are utilized to both image and ablate the breast cancer cells. Reproduced with permission.

Gold Colloidal Nanospheres

The final group of gold nanoparticles discussed for hyperthermiaapplications are gold colloidal nanospheres. Previously,these solid gold spheres were solely investigated fortheir use as imaging probes. However, the small sizeand relatively simple synthesis of these particles make themdefi ned as the portion of incident light being converted intophotothermal power by the nanoparticle, varied by less thana factor of three between the different particles studied. This fi nding suggests that no particular nanoparticle configurationhas signifi cant therapeutic advantage over the others.While there has been significant focus to date on identifyingideal gold nanoparticle configurations for photothermaltherapy, there are several additional promising research avenues for further optimization of the technology. The useof NIR light and nanoparticle absorbers in photothermaltherapy offers critical advantages, particularly in protectinghealthy tissue from thermal damage. However, solid tumorscan occur within the body at depths greater than 1 cm, whichis beyond the penetration of NIR light in tissue. In these cases,fi ber-optic probes often can be used to deliver light. In addition,the use of alternative irradiation modalities is an areaof recent signifi cant research activity and may be particularlyuseful for treating tumor locations that are diffi cult to access from the surface or through interstitial fi ber-optic devices.

Asecond area of current research activity is the optimizationof the delivery and biodistribution of gold nanoparticles invivo. To ensure therapeutic success, maximal gold nanoparticleaccumulation in the tumor is highly desirable. Furthermore, minimization of gold-nanoparticle accumulation withinnontarget organs such as the liver and spleen is ideal. Theuse of smaller nanoparticles enhances the blood half-life andimproves tumor accumulation and specifi city. However, it islikely that additional modifications beyond size optimizationwould be useful to further improve nanoparticle biodistribution, and this has become an area of expanding research. Afi nal area of current research activity is the identification ofany impact of the long-term presence of gold nanoparticlesin vivo. Relatively short-term studies have been performed todate with highly encouraging results. The remaining sectionsof this review will focus on discussing these areas of current.

Surface Enhanced Raman Scattring (SERS)

One advantage of gold nanoparticlesis the simplicity of modifying the nanoparticlesurface. By adding an antibodyor other small molecule to the nanoparticle surface thatcorresponds with the targeted cancer, it has been suggestedthat the specifi city of tumor accumulation and

tumor cellspecific binding could be increased. There have been manyin-vitro studies supporting this hypothesis. Loo et al. werethe fi rst to demonstrate increased specifi city of binding, darkfield imaging, and photothermal therapy in vitro using gold–silica nanoshellsmodified with an antibody to the HER2receptor, which is overexpressed in some breast cancersThe El-Sayed group subsequently demonstratedin-vitro cancer ablation using anti-EGFR-conjugatedgold nanorods. The specifi city of antibody-targeting fortherapy has been demonstrated with several other antibodiesin vitro, including antibodies for acute lymphoblastic leukemia, Pseudomonas aeroginosa, and medulloblastoma. Similar to tumor-specifi c antibodies, small molecules specifi cfor cancer cells have also been added to the surface of goldnanoparticles based on the hypothesis that these moleculeswill diffuse through tissue more efficiently than antibodiesbecause of their small size. Using folate-conjugated nanorods, Tong et al. demonstrated that more laser power was requiredto kill cells with internalized nanorods versus cells withsurface-bound nanorods in vitro.

This was also demonstratedusing gold nanorods conjugated to modifieddeltorphinpeptide. Other groups have used targeting moietiessuch as bombesin to specifically target breast and prostatecancers for imaging, arginine-rich peptides to promotespecifi city via nanoparticle internalization by the targetcells, and aptamers.

Despite the many in-vitro therapy demonstrations usingsurface-modified nanoparticles, in-vivo studies have not shownwidespread success in enhancing delivery. Eghtedari et al. comparedPEG- and anti-HER2-PEG-coated nanorods administeredto tumor-bearing mice. They presented qualitativedata in the form of histology to confirm that the addition of theantibody on the nanoparticle surface improved tumor accumulation.Li et al. combined gold nanorods targeted to eitherthe HER2 or EGFR receptor and photoacoustic imaging toshow that targeting enhanced the image contrast of squamousFor in-vivo targeting of the tumor vasculature, the use ofphage technology is proposed. Bacteriophage (phage) displaylibraries have been used to identify peptide ligands that specifically bind the integrins, proteoglycans, and other featuresunique to blood vessels undergoing angiogenesis.

These phages can be selected and used to target tumorblood vessels for imaging or drug delivery. In addition, when coupled with gold colloidal nanospheres, gold–phagehydrogels have been imaged using darkfield microscopy,fluorescence microscopy, and NIR surface-enhanced Ramanscattering spectroscopy. By coating the primary particlesdescribed by Tasciotti et al. with phages specifi c to angiogenicblood vessels, the primary particles could

be targetedto the tumor vasculature for margination, adhesion, and,ultimately, delivery of therapeutic particles. The tumor couldbe identified and imaged using the gold–phage hydrogelcoatings of the silicon microparticles, and then treated usingthe delivered nanoparticles, giving these vehicles theranostipotential.

Another vehicular strategy that has been demonstratedin the literature is the aptly named "trojan horse" methodGold–silica nanoshells were internalized inmacrophages by incubating the particles with the cells for 24 hand allowing uptake via phagocytosis. The nanoshell-loadedmacrophages infiltrated tumor spheroids in vitro after 3 daysof incubation and accumulated at the rim of the spheroid'score hypoxic region. Although this was not a signifi cantenhancement of tumor core penetration, there was a marginalincrease in the percentage of gold nanoparticles reaching thehypoxic core.Although the in-vitro studies for both of these deliverystrategies show some promising results, there have beenno in-vivo studies delivering gold nanoparticles to date. Inreality, no strategy discussed in this section has conclusively.

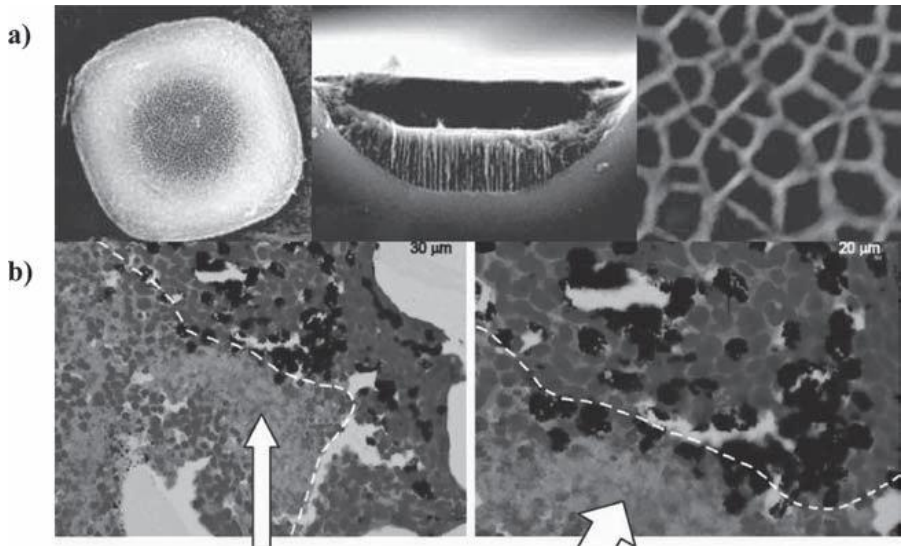

Figure 7 SERS.

Goodman et al. tested the effect of cationic (ammoniumfunctionalized)and anionic (carboxylate-functionalized)2 nm gold nanoparticles at different concentrations for 24 hand found that cationic nanoparticles were more cytotoxicthan the anionic. Although cytotoxicity has been seen forgold nanoparticles of 5 nm at concentrations in the micromolarrange, most gold nanoparticles used for therapy applicationsare larger than 25 nm, where the IC50 concentrationsare several orders of magnitude larger. In addition, for mostbiological

applications, the particles are PEGylated, whichprovides stability and protects cells from interacting with anysurface detergents used to stabilize the nanoparticle.

Properties Of Cancer Shells

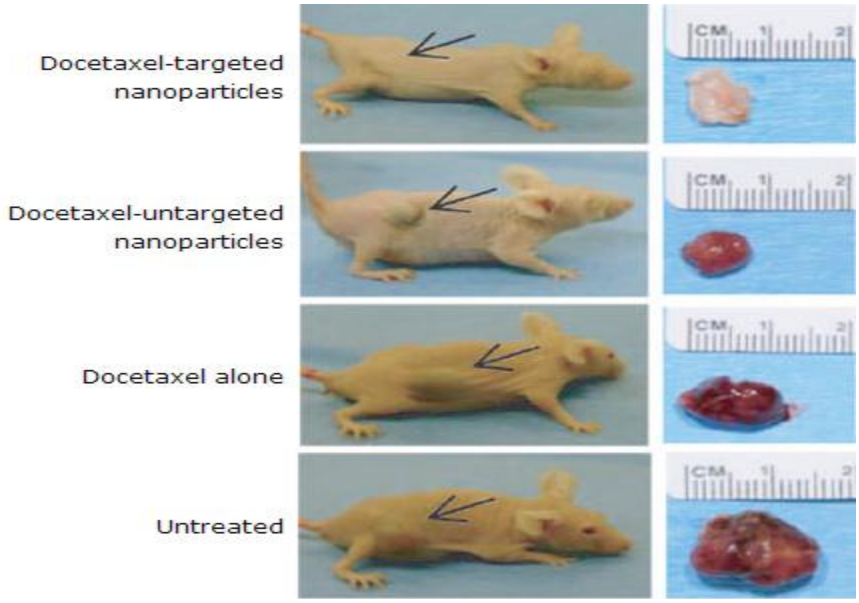

Figure 8 Experiment on mice bearing human prostate tumors.

- Epidermal Growth Factor Receptor (EGFR)over expression and over activity
- have been associated many differenttypes of Cancer.
- Cancer cells have a unique properties that can be exploited by nanoparticles
- Their rapid rate of growth causes them to intake an abnormal amount of nutrients (i.e., folic acid).
- Nanoparticles can be used to target bio-markers or antigens that are highly specific to Cancer cells.

Applications of Gold Nanoparticals of Cancer[19]

Gold nanoparticles has been successfully used as a therapy for

Rheumatoid arthritis

Alzheimer's disease

The administration of hydrophobic drugs require molecular encapsulation and it is foundthat nanosized particles are particularly efficient in evading the reticuloendothelial system**.**

Cancer detection

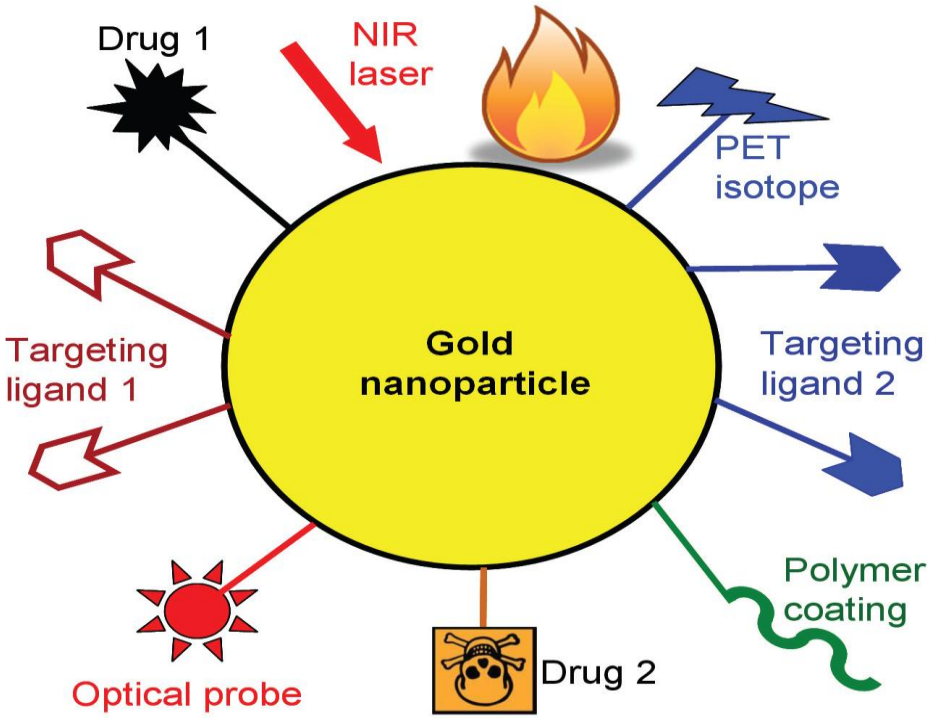

Fig. 9: Multifunctional gold nanoparticle-based platform incorporating multiple receptor targeting, multimodality imaging, and multiple therapeutic entities. Not all functional moieties will be necessary and only suitably selected components are needed for each individual application.

Background By Cancer[20]

Cancer is the third leading cause of death (after heart disease and stroke) in developedcountries and the second leading cause of death (after heart disease) in the United States. Because of the high death rate caused by cancer, plenty of research is going on in the field ofNanomedicine for Cancer diagnosis and therapy.

Tumor

Definition and Causes.

Definition

"Tumor is an abnormal growth of body tissue. It can be cancerous (malignant) or non-cancerous (benign)".

Causes

Generally tumors occur when there is a problem with the division of cells.

Inside our body. Normally, the division of cells in the body is strictly. controlledIf the balance ofcell division and death is altered, a tumor may form.

Problems with the body's immune system can lead to tumors. Tobacco causes moredeaths from cancer than any other environmental substance. Other causes include:
Benzene and other chemicals and toxins
Drinking excess alcohol
Excessive sunlight exposure
Genetic problems
Inactivity (sedentary lifestyle)
Obesity
Radiation.[2]

A cancerous cell surrounded by healthy tissue will reproduce at a higher rate than theother cells, thereby affecting the nutrient supply and elimination of metabolic waste products.Once a small tumor mass is formed, the healthy tissue will not be able to compete with thecancer cells as there is no sufficient supply of nutrients from the blood stream. Tumor cells willdisplace healthy cells until the tumor reaches a diffusion-limited maximal size. This diffusionlimitedmaximal size of most tumors is around 2 mm.Generally tumor cells do not initiate apoptosis (a cell suicide mechanism) in a lownutrient environment as they do require oxygen, glucose and amino acids (building blocks ofcell function). The healthy tissue which then becomes extinct did not demand high nutrients dueto its slower growth rate. Thus the tumor cells will continue dividing because they do so withoutregard to nutrient supply but at the same time many tumor cells will also perish due toinsufficient nutrients.

The tumor cells at the outer edge of a mass have the best access to nutrients whilecells on the inside die creating a necrotic (death of cells) core within tumors that rely on diffusionto deliver nutrients and remove waste products.In essence, a steady state tumor size forms, as the rate of proliferation is equal to therate of cell death until a better link with the circulatory system is created. To grow beyond thissize, the tumor must recruit the formation of blood vessels to provide the nutrients essential tofuel its continued expansion. shows the tumor development from a single cell to adiffusion-limited tumor.

There can be numerous tumors at this diffusion-limited maximal size throughout thebody. Until the tumor can gain that admission to the circulation it will remain at this size and

theprocess can take years. The exact molecular mechanisms that initiate angiogenesis (growth ofnew blood vessels from preexisting blood vessels) at a tumor site are not known and could beunique to the site of origin but more information about what factors play a role in this process isbeing discovered.

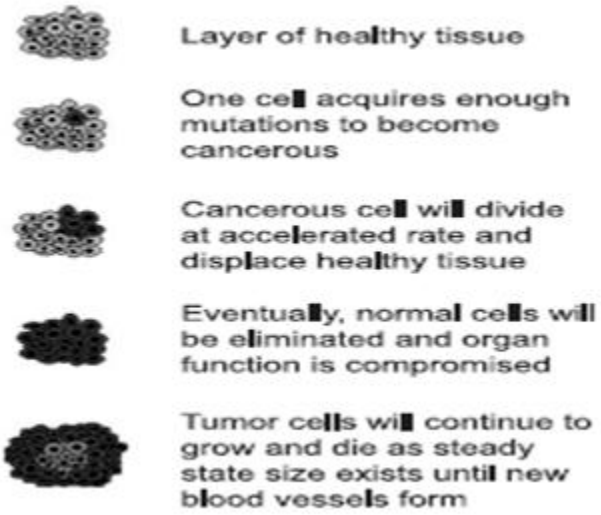

Figure 10. Tumor development from initial carcinogenesis to diffusion-limited maximal size.

Current Cancer Treatments

There are different types of treatment for patients with cancer. Some of the standardtreatments used are discussed as follows:

Surgery

Among all the treatments Surgery is the oldest form of cancer treatment. It as wellplays an important role in diagnosing cancer and finding out how far it has spread (this processis called staging). For many types of cancer, surgery offers the greatest chance for cure.

Thisworks best, especially for cancers that have not spread to other parts of the body. Majority ofthe people with cancer will have some kind of surgery.Preventive surgery: Preventive surgery is done to remove body tissue that is likely tobecome cancer, even though there are no signs of cancer at the time of the surgery. At time preventive surgery is used to remove an entire organ when a person has an inherited conditionthat puts them at a much higher risk for having cancer some day. For example, some women with a strong family history of breast cancer have a higher risk of getting breast cancer. In suchcases, these

women may want to consider prophylactic mastectomy i.e. the breasts areremoved before cancer is diagnosed.

Radiation Therapy

Radiation therapy is a cancer treatment that utilizes high-energy x-rays or other formsof radiation to kill cancer cells or keep them from growing. There are two types- of radiationtherapy

1. External radiation therapy and.
2. Internal radiation therapy. In External radiation.

Therapy a machine is used outside the body to send radiation toward the cancer. Internalradiation therapy uses a radioactive substance sealed in needles, seeds, wires, or cathetersthat are placed directly into or near the cancer. The way the radiation therapy is given dependson the type and stage of the cancer being treated.

Chemothrepy

Chemotherapy is a type of cancer treatment where drugs are used to stop the growthof cancer cells. These drugs either kill the cancer cells or prevent them from dividing.Chemotherapy is taken by mouth or by injecting it into the vein or muscle. These drugs gothrough the bloodstream and can reach cancer cells throughout the body. This is known assystemic chemotherapy. When chemotherapy is given directly into the spinal column, an organ,or a body cavity such as the abdomen, the drugs primarily affect cancer cells in those areas .This is known as regional chemotherapy.

Hormone therapy

Hormone therapy is a recently used treatment for cancer. In this type of treatmenteither the action of harmones are blocked or removed to stop the cancer cells from growing.Hormones are substances generated by glands in the body and circulated in the bloodstream.

Immunotherapy

Another recently used treatment for cancer is Immunotherapy. In this, patients aregiven medication to stimulate the body's immune system to fight cancerous cells.

Limitations on Current Cancer Treatments

All cancer treatments come with benefits, risks, and side effects. The types and intensity of sideeffects differ from person to person and with the type and location of the cancer, and theperson's health. Downside of the current cancer treatment methods are discussed below.

1. Radiation therapy Limitations

As radiation is a local treatment, side effects depend on the area of the body beingtreated. Some of the most common side effects are minor burns, skin changes, fatigue, loss ofappetite, nausea, vomiting, weakness, and lowered resistance to infections

2. Cancer Surgery Limitations

Common side effects of cancer surgery are: pain, swelling around the site of surgery, bleeding, bruising around the site of surgery, infection, fatigue, loss of appetite, etc.

3. Chemotherapy Limitation

Following are the common chemotherapy side effects that are common to severalclasses of chemo agents: nausea and vomiting, hair loss, fatigue, reduced blood levels of redblood cells, white blood cells or platelets, reduced or absent menstruation (periods) in women,changes in thinking and memory, sore and inflamed throat and mouth, brittle or discolored nails,diarrhoea or constipation, etc. Some long term side effects could be permanent organ damageto heart, lung, liver, kidneys, or reproductive system. In some people cognitive functions (suchas thinking, concentrating, and memory) remain a challenge even after months or years aftertreatment. In addition, nervous system changes can develop months or years after the treatment.

4. Hormone Therapy Limitations

In Hormone therapy certain drugs have a high risk of developing a blood clot. Hormonetherapy for prostate cancer can cause impotence. Hormone treatment for breast cancer cancause hot flushes and abnormalities in menstruation.

5. Immunotherapy Limitations

Some of the common immunotherapy side effects include itches and irritation aroundthe injection area. Some other less common immunotherapy side effects are major swelling,bruising, cold, asthma or hay fever symptoms in a few hours after the injection and increasedtiredness in the proceeding days after having the injection.

In the recent years, Gold nanoparticles (AuNPs or GNPs) have been brought to thefront position of cancer research because of their simplistic synthesis procedures, rich surfacechemistry, strongly enhanced and tunable optical properties and exceptional biocompatibility.High quality, yield and size controllable AuNPs can be prepared from simple citrate reductionmethod. We can also make different shapes of AuNPs like gold nanorods, gold nanoshells, hollow gold nanoparticles etc. These different shaped AuNPs show large red shift properties, thereby making them favorable candidates for Cancer Therapy.

Uses in Treatment[21]

Cancer cells die at 42° C (108° F), normal cells die at about 46° C (115° F).

Current optical fiber treatmentHollow, gold nanospheres are 50 times more effective at absorbing light near theinfrared than solid gold nanoparticlesNanoparticles can be tuned to be excited only by certain ranges of light In another study, pre-clinical trials reveal that a single intravenous nanoparticleinjection eradicated 100 percent of tumors in mice when exposed tonear-infrared light.Most work is being done with near-infrared light, which is harmless to humans butcan only penetrate human tissue about 1.5 inches. Nanoparticles heated upto 70° C (160° F) The Kanzius RF Machine uses radio waves for dielectric heating.

Fig. 11: Kanzius RF Machine.

Future Research And Scope[22]

Human clinical trials within the next 2-3 years.Highly specific team of communicating multifunctional nanoparticles usedin the discovery, treatment, and prevention of Cancer

growth Safer, more consistent, and highly specific nanoparticle productionTurning Cancer into a chronic, but manageable disease within the next15-20 years.

T here has recently been a great deal of interest in thescientific community concerning the application ofnanotechnology in medicine. One particularly exciting field of research involves the use of gold nanoparticles in thedetection and treatment of cancer cells (Soppimath, Betageri,& Cho, 2008). Current methods of cancer diagnosis andtreatment are costly and can be very harmful to the body.Gold nanoparticles, however, offer an inexpensive route totargeting only cancerous cells, leaving healthy cellsuntouched . The unique lightabsorption and emission characteristics of gold nanoparticleshave made them one of the most studied entities in recentcancer diagnostic research. Research has found that,when gold nanoparticles are subjected to light, the light isscattered in a highly specific pattern. These specific patternsare determined by the orientation of the nanoparticles.

The diagnosis of cancer is an area in which the lightabsorption and emission characteristics of gold nanoparticleshave become a key advantage. It has been proposed thatthese aspects of gold nanoparticles themselves can be utilizedin the diagnosis of cancerA currently developing technique involvesattaching a specialized antibody that is attracted to cancerouscells to the end of a gold nanoparticle, and mixing thiscompound with blood or tissue samples containing cancerouscells. The blood or tissue samples are then subjected to whitelight and examined using standard microscopy. Since eachtype of cancer has a unique protein on its cell surface, thegold nanoparticles will be oriented differently, depending onwhich type of cancer cells they have been attached to. Thisresults in each type of cancer having its own unique patternof scattered light. Doctors would then be able to determineboth the location and type of cancer with this method.

Gold nanoparticles have a high usability level whencompared to other similar methods of cancer detection.

One of these other methods employs quantum dots instead of goldnanoparticles to illuminate the location of cancerous tissue.The problem with these quantum dots, however, is that theyburn out after extended exposure to light .Gold nanoparticles, on the other hand, will not burn out afterextended light exposure, allowing them to illuminatecancerous cells for much longer periods of time then thequantum dots . Gold nanoparticleluminescence is also a more highly sensitive technique,permitting doctors to use fewer chemical markers in order toobtain

the same information.As well as being able to diagnose cancer, goldnanoparticles have the potential to treat cancer without anyof the harmful side effects associated with current treatmentmethods. Two of the most common forms of cancertreatment, chemotherapy and radiation therapy, are bothextremely aggressive and can have fatal side effects even onyoung and otherwise healthy individuals. Side effects withthese treatments occur because healthy cells are killed alongwith diseased cells in an effort to rid the body of cancer.

Two very promisingmethods of cancer treatment involving gold nanoparticles arecurrently being investigated for their ability to target onlycancerous cells while leaving healthy cells unharmed. The first method utilizesgold nanoparticles to absorb light in the near-infraredwavelength range and the second involves a synthesis of chemotherapy and gold nanoparticles.The first possible method of treatment is based on goldnanoparticles that have either a trigonal pyramidal or starshape. These specific shapes are extremely efficient atabsorbing near-infrared light and turning it into heat. Theproposed procedure is to attach a cancer-attracted protein tothese triangular or star-shaped gold nanoparticles in order tohave the nanoparticles "stick" to the cancer cells, as they doin the cancer detection method. Meanwhile, they have nointeraction with healthy cells.

Once the gold nanoparticles are attached, the cancerouslocation is subjected to a highly concentrated beam of near.infra-red light from an external source. This combination willcause the gold nanoparticles to heat up enough that they willactually 'cook' the cancerous cells. Even though thecancerous cells will be destroyed, there will be little or nodamage to surrounding cells since the infra-red light isharmless to any cells without an attached gold nanoparticle.Although this method is completely non-invasive, it doesrequire the cancer to be relatively near to the surface of thepatient's body in order for the gold nanoparticles to absorbenough of the light to kill the cancer cells. This method is a technologically evolved form of aprocedure that is currently being used called photoablationtherapy (PAT). Unfortunately, current PAT techniques usesuch high frequency lasers to burn cancerous cells that theyare very dangerous to the skin of the patient and are notalways a viable option. Overall, theeffectiveness, inexpensiveness, and safety of using goldnanoparticles make them an ideal candidate for use in nextgeneration PAT.

The other method involving gold nanoparticles thatscientists are hoping to use in the treatment of cancer is theirsynthesis with chemotherapy. In 2007, scientists found thatgold nanoparticles in the shape of 'nanorods' were able topenetrate the cell membrane. They

wanted to use thistechnology to help deliver chemotherapy in small dosesdirectly to cancer cells, as opposed to subjecting the entirebody to harmful chemotherapy.Unfortunately, this proved to be an ineffective deliverymethod due to the nanorods being too bulky for sufficientcell membrane penetration. More recently, in 2009, scientistsfabricated a gold nanoparticle in the shape of a sphere. Thisnew shape greatly increased the rate of cell penetration bythe nanoparticles when compared to the larger and less agile‘nanorods’. Chemists used this newdiscovery to pair spherically shaped gold and iron oxidenanoparticles together into a ‘dumbbell’ formation, attaching a cancer-detecting molecule on one side and a cancerfightingmolecule to the other.

Cisplatin, apowerful anticancer drug, is fixed to the gold nanoparticle,and Herceptin, an antibody that specifically seeks out breastcancer cells, is applied to the iron oxide.Once the Herceptin end of the compound locates a cancer\cell, the spherical gold nanoparticle is able to penetrate themembrane and enter the cell, taking the small Cisplatinmolecule along with it. As the gold-Cisplatinnanocompound enters the cell, the sudden drop in intracellular pHcauses the Cisplatin molecule to be hydrolyzed and separatedfrom the gold nanoparticle . The cancer cellis now treated internally so as not harm any of thesurrounding cells. Although this test was specificallytargeted at breast cancer using Herceptin, the same techniquecan be employed against any type of cancer as long as it hasan active antibody. As with the other treatment method, themain appeal of this technique is that the cancer treatment canbe applied locally and non-invasively, and has the ability tonot only treat the cancer, but detect and illuminate it as well.

Nanoscience has had a huge impact in medicine in recentyears due to its non-invasive applications. The use of goldnanoparticles to diagnose and treat cancer has been, and willcontinue to be, on the forefront of this exciting research.While cancer detection using gold nanoparticles in commonmedical practice is just around the corner treatment using gold nanoparticlephotothermal ablation and nano-chemotherapy will be inclinical trials for some time before they are being used onpatients regularly. With nanotechnology advancing as fast asit currently is, scientists will hopefully be able to utilize thecharacteristics of compounds such gold nanoparticles in thedetection and treatment of mmany more deadly diseases in theyears to come.

Summary[23]

Metastasis is still an extremely complex disease with multiple questions stillremaining. While 90% of human cancer deaths are due to cancer metastases, thehope for fighting cancer is sustained by the fact that there were more than 50 newagents approved in the past 10 years for cancer treatment and hundreds of newagents in clinical development. The development of nanoparticle drug deliverysystems is expected to have a big impact on the clinical approaches for cancertherapy. The ability to specifically target nanoparticles along with the controlleddelivery of a therapeutic payload provides powerful new ways to treat cancer whichare only starting to be realized. By rationally designing nanoparticles based on improved knowledge of cancer biology and the tumor microenvironment, improvedefficacy can be achieved. In addition, multifunctional nanoparticles able to carryimaging agents and deliver multiple drugs are now being developed for enhanceddetection and treatment of cancer. The application of nanotechnology to cancer hasalready produced some exciting results and holds even greater promise for cancerpatients in the future.

Plasmonic gold nanostructures thus show great promise forthe selective PTT for cancer as well as other diseases. Wepropose the name PPTT for this treatment. It is realized thata number of variables need to be further addressed, e.g.,stability, biocompatibility, and chemical reactions of nanoparticlebioconjugates in physiological environments, bloodretention time, tumor extravasation, the fate of the nanoparticlesfollowing therapy, etc. We anticipate that thesuccess and promise of the initial use of plasmonicnanoparticles for selective PPTT could be efficientlyextended to clinical stage once the optimal parameters ofthese variables are identified, as is being done through -Different types of Cancer cells have unique properties that can beexploited by nanoparticles to target the Cancer cells-Nanoparticles can be used to detect/monitor (by utilizing or adding optic,magnetic, and fluorescent properties) and to treat Cancer (by Heat ablation,chemotherapy, gene therapy).-No human trials have been performed yet and human trials are still atleast a few years away. (Unknown side effects, toxicity, difficulty inmanufacturing and harmful byproducts, need for highly specificnanoparticles)Multifunctionality is the key advantage of nanoparticles overtraditional approaches. Targeting ligands, imaging labels,therapeutic drugs, and many other functional moieties canall be integrated into the nanoparticle conjugate to allowfor targeted molecular imaging and molecular therapy of single modality is perfect and sufficient to obtain all thenecessary information for a particular question . For example, it is diffi cult to accuratelyquantify optical signal in living subjects, particularly in deep tissues; Radionuclide-

based imaging techniques (eg, positronemission tomography [PET]), are very sensitive and highlyquantitative but they have relatively poor spatial resolution.

CONCLUSION

Combination of certain imaging modalities can offer synergisticadvantages over any single modality alone. Dual-modality agents that combine PET, which is very sensitive and highly quantitative (Phelps 2000),and optical imaging, which can significantly facilitate ex vivovalidation of the in vivo data, should be of particular interestfor future biomedical research. The relatively large size ofthe gold nanoparticle may potentially allow for simultaneousmultiple receptor binding of the targeting ligands onthe same particle. Thus, targeting multiple closely-related with in vivo diagnostics (noninvasive imaging before, during,and after treatment) can provide a synergistic approach thatneither strategy alone can offer. Upon further developmentand validation, nanoparticle-based approaches (both ex vivonanosensors and in vivo imaging) will eventually be ableto predict which patients will likely respond to a specifi cmolecular therapy and monitor their responses to personalizedtherapy. With the capacity to provide enormous sensitivity, throughput, and flexibility, nanotechnology has thepotential to profoundly impact cancer diagnosis and patientmanagement in the near future. Big strides have been madeand many proof-of-principle studies have been successfullyperformed, the future looks brighter than ever yet many hurdles remain to be conquered.

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