Review Article

Nanogoldtechnology-imaging, sensing and target therapy in head and neck cancer

Nishat Sultana, Suraksha Bhat Shenoy, M. E. Sham[1], Shilpa Keshav, Rachna Kaul

Departments of Oral Medicine and Radiology, and [1]Maxillofacial Surgery, Vydehi Institute of Dental Sciences, Bangalore, India

ABSTRACT

Innovation in the last decade has endowed nanotechnology with an assortment of tools for delivery, imaging, and sensing in cancer research. Cancer nanotherapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. To improve the biodistribution of cancer drugs, nanoparticles have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of themainmediators ofmultidrug resistance, resulting in the increased intracellular concentrationof drugs.Multifunctional andmultiplex nanoparticles are nowbeing actively investigated and are on the horizon as the next generation of nanoparticles, facilitating personalized and tailored cancer treatment.

Keywords: Cancer, gold nanoparticles, nanotechnology

INTRODUCTION

Until recently, prevention, diagnosis and treatment of cancer have been considered separately. The lack of interaction between these fields has hampered efforts to deal with cancer effectively. Because of this, it has recently been necessary to design a new paradigm that simultaneously combines the diagnosis and therapeutics of cancer as one.[1,2] Nanoparticle-based imaging and therapy using iron oxide, quantum dot, silica and gold are of interest to theranostic nanomedicine.[3] These rapidly emerging tools are indicative of a burgeoning field ready to expand into medical applications.

WHAT ARE NANOPARTICLES?

The prefix of nanotechnology derives from 'nanos,' the Greek word for dwarf. A nanometer is a billionth of a meter, or to put it comparatively, about 1/80,000 of the diameter of a human hair. Nanoparticles are typically smaller than several hundred nanometers in size, comparable to large biological molecules such as enzymes, receptors and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules, both on the surface of and inside the cells, which may revolutionize cancer diagnosis and treatment.[4]

Because of their size range, 10–100 nm, nanoparticles are very suitable for manipulations at the molecular level, for example, cell-receptor binding for site-selective imaging and targeting, localization of encapsulated therapeutics for delivery, and decoration of expression systems for substrate-based nanosensing.[4]

Historically, the first method of nanoparticle production was developed by Rirrenbach(1973) and Speiser (1976).[5] Later, Kopf *et al.*, (1976, 1977) used it for the entrapment of drugs. This process is obsolete for medical purposes because of the high amounts of hydrocarbons and surfactants needed and because of the non-biodegradability of the polymer (polyacrylamide). This process was improved by Giamalidis, Ekman and Sjoholm 1978, Krause *et al.m* 1986, Gasco and Trotta 1986 and many more.[6]

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.95012

Address for correspondence: Dr. Nishat Sultana, No-37, 1st Cross, Silver Oak Street, JP Nagar, 7th Phase, Bangalore – 78, India.
E-mail: nishat_tamanna9@rediff.com

The most well-studied nanoparticles include quantum dots,[7,8] carbon nanotubes[9] paramagnetic nanoparticles,[10] liposomes,[11] gold nanoparticles[12] and many others[13,14] [Figure 1].

One of the major applications of nanotechnology is in biomedicine. Nanoparticles can be engineered as nano platforms for effective and targeted delivery of drugs and imaging labels by overcoming the many biological, biophysical, and biomedical barriers.[15]

Other applications of nanotechnology are, fluorescent biological labels, gene delivery, biodetection of pathogens, probing of DNA structure, tumor destruction via heating(hyperthermia), separation and purification of biological molecules and cells, magnetic resonance imaging contrast enhancement and phagokinetics studies.[16] Among them, gold nanoparticles (AuNPs) have been extensively used as drug delivery carriers, cell-targeting vectors, sensors and molecular imaging of cancer cells due to their stability, ability to bind to biomolecules via AueS bonds, surface plasmon absorption and light-scattering properties.[17]

SYNTHESIS OF GOLD NANOPARTICLES

There are many subtypes of gold nanoparticles based on the size, shape, and physical properties. [Figure 2] The earliest studied gold nanoparticles are gold nanospheres (although not exactly spherical in a strict sense). Subsequently, nanorods, nanoshells and nanocages have all been reported. Another type of gold-based nanoparticles, with excellent surface enhanced Raman scattering properties are termed "SERS nanoparticles".[15]

Gold nanospheres (also known as gold colloids) of 2 nm to over 100 nm in diameter can be synthesized by controlled reduction of an aqueous HAuCl4 solution using different reducing agents under varying conditions. The most commonly used reducing agent is citrate, which can produce nearly monodisperse gold nanospheres.[18] The size of the nanospheres can be controlled by varying the citrate/gold ratio. Generally, smaller amount of citrate will yield larger nanospheres. The major limitations of this method are the low yield and the restriction of using water as the solvent.[15]

Several other methods have been investigated for gold nanosphere synthesis such as the use of other reductants or ligands.[19,20] There are a number of literature reports on the use of dendrimers as templates or stabilizers for gold nanosphere preparation.[21-23] The size and shape of the gold nanospheres could be readily controlled by tuning the synthesis parameters such as the block composition and the relative/absolute concentrations of the block copolymer and HAuCl4.[15]

Growth of gold nanospheres in human cells has also been reported.[24] Typically, gold nanospheres display a single absorption peak in the visible range between 510 nm and 550 nm. With increasing particle size, the absorption peak shifts to a longer wavelength and the width of the absorption spectra is related to the size distribution range.[15]

BIOMEDICAL APPLICATIONS OF GOLD NANOPARTICLES

Cancer nanotechnology is an interdisciplinary area with broad potential applications in fighting cancer, including molecular imaging, molecular diagnosis, targeted therapy and bioinformatics. Gold nanoparticles have been investigated in diverse areas such as *in vitro* assays, *in vitro* and *in vivo* imaging, cancer therapy and drug delivery.

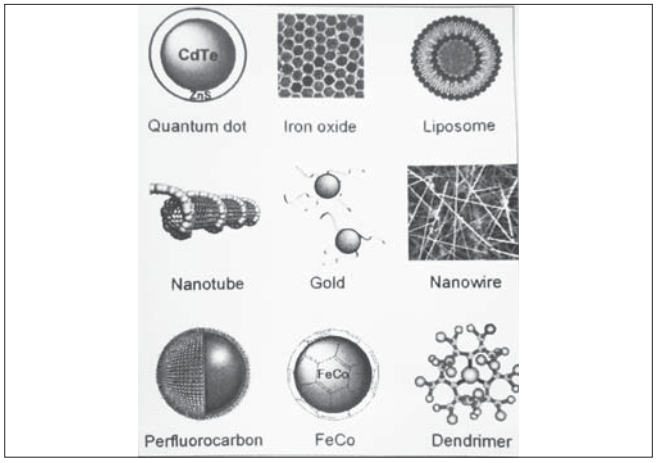

Figure 1: Different types of nanoparticles used in biomedical application for target therapy

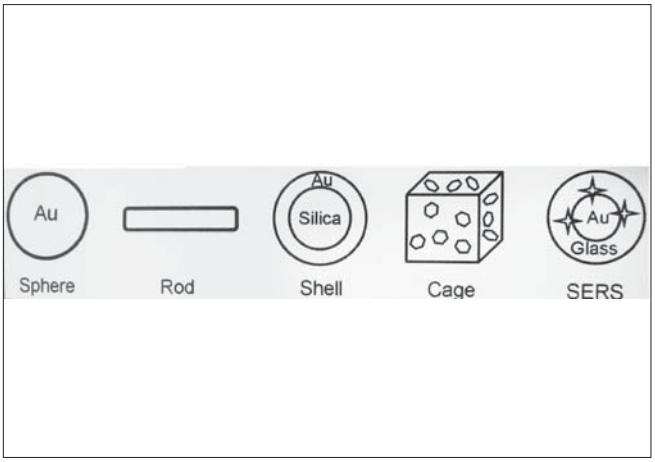

Figure 2: Different types of gold particles

IMAGING

To date, most imaging studies using gold nanoparticles were carried out in cell culture. The versatile optical properties of gold nanoparticles have enabled optical imaging of cells and phantoms with a wide variety of contrast mechanisms. Peleg *et al*.,[25] reported functional cellular imaging around single molecules, taking advantage of the enhanced second harmonic signal by antibody-conjugated gold nanospheres. Subsequently, many other studies have been reported, which employed photothermal interference contrast,[26] AFM,[27] dark-field imaging,[28,29] reflectance imaging,[30,31] as well as fluorescence and scanning electron microscopy.[32] Two-photon luminescence imaging of cancer cells in a 3D tissue phantom down to the 75 μm depth has been achieved using gold nanorods. Fluorescent dyes have been conjugated to gold nanoparticles for fluorescence imaging of cells, upon additional modification with certain targeting ligands.[33] The advantage of imaging the gold nanoparticle itself is that there is no photobleaching or blinking, which is inherent to many other fluorophores, However, the disadvantage is that the optical signal of gold nanoparticles may not be as strong as certain fluorescent dyes or quantum dots.[15]

Nanoshell-enhanced optical coherence tomography (OCT) has the potential for molecular imaging and improved detection of diseases. Recently, *in vivo* imaging using gold nanoparticles as contrast agents has been reported.[15] Photoacoustic tomography (PAT) is a hybrid imaging modality that uses light to rapidly heat elements within the tissue, which results in photoacoustic waves (generated by thermoelastic expansion) that can be detected with an ultrasonic transducer. The use of near infrared region absorbing gold nanoparticles can significantly enhance the image contrast, due to the more substantial differences in optical absorption (hence stronger photoacoustic wave generation) than the endogenous tissue chromophores. With photoacoustic imaging, multiple molecular targets have been detected simultaneously using different monoclonal antibodies conjugated to two types of gold nanorod with different aspect ratios (which have peak optical absorption at different wavelengths).[34] Recently, *in vivo* imaging using gold nanoparticles as contrast agents has been reported.

IN VIVO IMAGING

Many paramagnetic nanoparticles have been used for magnetic resonance (MR) imaging, both preclinically and clinically.[35] Au3Cu nanoshells were reported to be capable of enhancing the contrast of blood vessels *in vivo*, which suggested their potential use in MR angiography as blood pool agents. However, due to the low sensitivity of MRI, a dose-dependent toxic effect of the nanoshells in mice was observed.[36] But gadolinium-doped gold speckled silica nanoparticles have been shown to produce a strong magnetic resonance and photoacoustic tomography contrast.[37] Raman spectroscopy is the most promising imaging technique for gold nanoparticle-based contrast agents. The Raman spectra and Raman images of methylene blue molecules adsorbed as a single layer on gold nanospheres were found useful for studying the plasmon properties. Later, antibody-conjugated gold nanorods were reported to give a Raman spectrum that is greatly enhanced, sharpened and polarized.[38,39] Raman imaging was tested in cells but not in living subjects.[39] *In vivo* targeted imaging of cancer using Raman spectroscopy and SERS nanoparticles has been reported [Figure 3]. Small molecule Raman reporters (such as fluorescent dyes) were stabilized by thiolated Polyethylene glycol and gave large optical enhancements. When conjugated to tumor-targeting ligands, the conjugated SERS nanoparticles were able to target tumor markers such as epidermal growth factor receptor (EGFR) on human cancer cells and in xenograft tumor models.[40] SERS nanoparticles composed of a gold core, a Raman-active molecular layer, and a silica coating were used for Raman imaging *in vivo*.[41] Raman imaging holds significant potential as a strategy for biomedical imaging of living subjects. However, one has to keep in mind that optical imaging in mice can not be directly scaled up to *in vivo* imaging in human applications due to the limited tissue penetration of optical signal. In clinical settings, optical imaging (including Raman spectroscopy) is only relevant for tissues close to the surface of the skin (for example, breast imaging), tissues accessible by endoscopy (such as the esophagus and colon), and intraoperative visualization (typically, image-guided surgery).[15] Optoacoustic tomography is a novel medical imaging method that uses optical illumination and ultrasonic detection to produce deep tissue images based on their light absorption. Abnormal angiogenesis in advanced

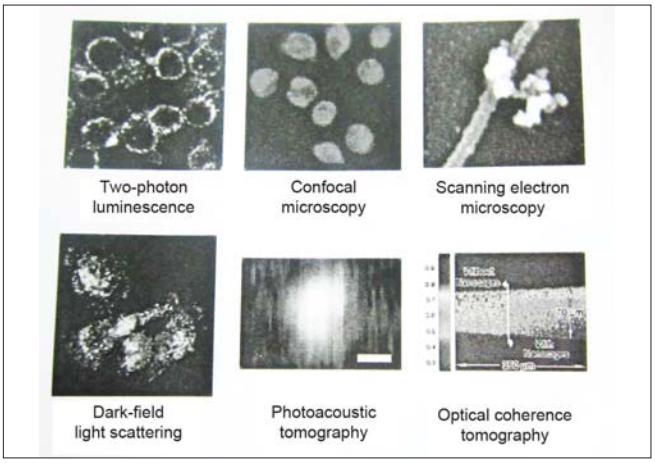

Figure 3: Gold nanoparticles have been investigated for cell and phantom imaging using various techniques (adapted from Chen *et al* 2005,Yaang *et al* 2005, de la Fuente *et al* 2006, Durr *et al* 2007, Li *et al* 2007a, oyelere *et al* 2007

tumors, that increases the blood content of the tumor, is an endogenous contrast agent for optoacoustic tomography. In early stages, however, angiogenesis is not sufficient to differentiate a tumor from normal, justifying the application of an exogenous contrast agent.

The development of a molecular based contrast agent composed of gold nanoparticles conjugated to a monoclonal antibody that improves optoacoustic tomography imaging potentiates its use in imaging deep tumors in early stages of cancer or metastatic lesions.[42] Gold conjugates can be delivered topically for imaging throughout the whole epithelium. These contrast agents have The potential to extend the ability of vital reflectance microscopies for *in vivo* molecular imaging.[30]

IN CANCER THERAPY

In the search for successful cancer treatment is the quest for the ultimate cancer therapeutic. Although conventional treatment options such as chemotherapy and radiation have experienced many advances over the past decades, cancer therapy is still far from optimal. Effectiveness of cancer therapy depends on a fine ratio that is determined by the ability of the therapeutic to eradicate the tumor while affecting as few healthy cells as possible. In this case, systemically administering bolus doses of powerful chemotherapeutics often results in intense side effects due to the action of the drugs on sites other than the intended target. To alleviate this difficulty, decades of research have focused on developing cancer-specific drugs or delivery systems that can preferentially localize existing agents to the tumor site. Recent advances in nanotechnology promises further developments in target-specific drug delivery systems. Commonly defined nanoparticle vectors include: liposomes, micelles, dendrimers, solid lipid nanoparticles, metallic nanoparticles, semiconductor nanoparticles and polymeric nanoparticles, although the scope of nanoparticle formulations that have been applied to cancer therapy is far more elaborate.[43]

LIPOSOMES

Early liposomes, designed as carriers inside their hydrophilic core or within their hydrophobic phospholipid bilayer coat, have shown promise in improving the solubility of many amphiphilic drugs, enhancing the transfer of therapeutics into cells and tissues, avoiding particular organs (e.g., brain, heart, kidneys), and enabling sustained release to reduce drug toxicity. Shielding from the mononuclear phagocytic system has been achieved by pegylation (addition of PEG). Liposomes have excellent biocompatibility and, after rupture, are readily integrated into cell walls, while the PEG is readily excreted. Current clinical usage of stealth liposomal doxorubicin takes advantage of organ avoidance and slow release to reduce toxicity effects.[6] Ishida *et al.*,[44] reported that 100–200 nm PEG-liposomes had the longest circulation time and greatest tumor accumulation in mice. Because of their ability to target immune-system proteins,[45] liposomes can also simulate amplified macrophage response during infection or introduction of toxins; they have, therefore, been used in vaccination[46] and as adjuvant therapy[47] during cancer treatment to boost the immune system.

DENDRIMERS

Dendrimers are hyper-branched synthetic macromolecules with highly controllable sizes, because of the uniform stepwise reactions used to achieve generational growth. The prospect of incorporating dendritic ligands on a nanoparticle surface is an attractive solution for maximizing binding efficiency and releasing drug molecules at each binding event. Such a cluster effect has been introduced with an emerging class of metal-binding nanoparticle-cored dendrimers containing nanogold for drug delivery.[48] A synergistic approach to encapsulating drugs whose diffusional release profiles can be tailored through controlling the dendrimer void sizes by limiting the generation number, binding the central core with nanogold or other nanoparticles for Infrared-activated release, ligand decoration and pegylation for active targeting and prolonged circulation times, is expected to provide an efficient system with exquisite dimensional control for therapeutic delivery.[6]

VIRAL NANOPARTICLES

Viruses have long been envisaged as nanoparticle vectors suitable for drug delivery, vaccines, and gene therapy, by harnessing their fusogenic cell receptor-binding properties and unsurpassed transfection efficiency.[49] A major thrust in cancer therapy involves the development of viruses for oncolytic activity. Oncolytic viruses are engineered to replicate selectively within cancer cells and induce toxic effects such as cell lysis and apoptosis, by mechanisms that exploit tumor selectivity, by use of intrinsically tumor selective viruses, gene deletion, replication-selective gene insertion, and modification of the virus coat.[50] A variety of viruses including cowpea mosaic virus, cowpea chlorotic mottle virus, canine parvovirus, and bacteriophages have been developed for biomedical and nanotechnology applications that include tissue targeting and drug delivery.[51] Several ligands or antibodies including transferrin, folic acid, and single-chain antibodies have been conjugated to viruses for specific tumor targeting *in vivo*.[52] By targeting heat shock protein, a dual-function protein cage with specific targeting and doxorubicin encapsulation has been developed.[53]

CARBON NANOTUBES

Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, diagnostic devices for the discrimination of different proteins from serum samples, and carriers to deliver vaccine or protein.[54] Antifungal agents (amphotericin B) or anticancer drugs (methotrexate) have been covalently linked to carbon nanotubes with a fluorescent agent (FITC). In an *in vitro* study, drugs bound to carbon nanotubes were shown to be more effectively internalized into cells compared with free drug alone and to have potent antifungal activity.[55,56]

TARGETED DELIVERY OF NANOPARTICLES

Ideally, for anticancer drugs to be effective in cancer treatment, they should first, after administration, be able to reach the desired tumor tissues through the penetration of barriers in the body with minimal loss of their volume or activity in the blood circulation. Second, after reaching the tumor tissue, drugs should have the ability to selectively kill tumor cells without affecting normal cells with a controlled release mechanism of the active form. These two basic strategies are also associated with improvements in patient survival and quality of life by increasing the intracellular concentration of drugs and reducing dose-limiting toxicities simultaneously. Increasingly, nanoparticles seem to have the potential to satisfy both of these requirements for effective drug carrier systems.[51]

SIZE

The size of nanoparticles used in a drug delivery system should be large enough to prevent their rapid leakage into blood capillaries but small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system, such as the liver and spleen. The size of nanoparticles should be up to 100 nm to reach tumor tissues by passing through the two particular vascular structures.[57]

Shape and characteristic: Nanoparticles should ideally have a hydrophilic surface to escape macrophage capture. This can be achieved in two ways: coating the surface of nanoparticles with a hydrophilic polymer, such as PEG, protects them from opsonization by repelling plasma proteins; alternatively, nanoparticles can be formed from block copolymers with hydrophilic and hydrophobic domains.[58]

PASSIVE TARGETING BY NANOPARTICLES

Enhanced permeability and retention effect: Fast-growing cancer cells demand neovascularization to supply them with oxygen and nutrients. Because of imbalance of angiogenic regulators, tumor vessels result in highly disorganized and dilated with numerous pores showing enlarged gap junctions, between endothelial cells and compromised lymphatic drainage, which enhances the permeability of macromolecules, including nanoparticles with molecular wt 50kDa, which can selectively accumulate in the tumor interstition.[59]

TUMOR MICROENVIRONMENT

Because of high metabolic rate of fast-growing tumor cells, the normal supply of oxygen and nutrient is not sufficient to maintain this. Therefore, tumor cells use glycolysis to maintain it, resulting in an acidic environment. The pH-sensitive liposomes are designed to be stable at a physiologic pH of 7.4, but degraded to release active drug in target tissues in which the pH is less than physiologic values, such as in the acidic environment of tumor cell.[60]

ACTIVE TARGETING BY NANOPARTICLES

The recent development and introduction of a wide variety of liposomes and polymers as drug delivery carriers increases the potential number of drugs that can be conjugated to targeted nanoparticles without compromising their targeting affinity relative to earlier antibody-drug conjugates. Taking advantage of this array of carriers, targeting moieties, and drugs, many recently developed active targeting drug conjugates use a ternary structure composed of a ligand or antibody as a targeting moiety, a polymer or lipid as a carrier, and an active chemotherapeutic drug.[51]

POTENTIAL OF NANOPARTICLES TO OVERCOME DRUG RESISTANCE

Drug resistance has emerged as a major obstacle limiting the therapeutic efficacy of chemotherapeutic agents. Among several mechanisms of drug resistance, P-glycoprotein is the best known and most extensively investigated. It has been suggested that nanoparticles may be able to circumvent P-glycoprotein–mediated resistance. One possible mechanism is that nanoparticles may avoid recognition by the P-glycoprotein efflux pump by means of being enveloped in an endosome when entering the cell, leading to high intracellular drug concentrations.[61]

ORAL COMPLICATIONS OF TARGETED CANCER THERAPIES

The side effects from targeted cancer therapies are considered to be mild to moderate, and in most cases

substantially less than conventional cancer chemotherapy. If targeted therapies are combined with conventional cancer therapies, previously identified toxicities may be increased in severity or duration. Additionally, adverse events that were unexpected in the preclinical setting may occur.[62]

Oral manifestations of targeted therapies may be independent or additive to oral complications in radiation and conventional chemotherapy. Oral mucositis may present with broad areas of erythema, aphthous-like stomatitis, or compound mucositis associated with conventional therapy.[63]

Cetuximab (Erbitux, ImClone) is a recombinant human/murine mAbs directed toward EGFR and is FDA approved in the United States, Canada, EU, and multiple other countries for treatment of head and neck squamous cell carcinoma (HNSCC) and colorectal cancer (CRC). Oral toxicities reported include mucositis, xerostomia, dysphagia, and pharyngitis. Although oral mucosal manifestations that limit therapy have not been associated with use of targeted therapies alone, mucosal damage may impact quality of life, oral intake, and may be painful, particularly when multi-modality therapy is employed. While prospective studies assessing oral complications of targeted therapies are lacking, initial studies have indicated oral complications may include oral mucosal inflammation and ulceration, dry mouth, and taste change, which may have impact upon quality of life and nutritional and caloric intake.[64]

FUTURE DIRECTION AND OPPORTUNITIES

Together with the progression of nanoscale drug delivery systems, advances in nanoscale imaging suggest the potential for the development of multifunctional ''smart'' nanoparticles that may facilitate the realization of individualized cancer therapy. Almost all types of nanoparticles have been evaluated for their suitability as multifunctional nanoparticles that can be applied for simultaneous *in vivo* imaging and treatment of cancers. Eventually, multiplex nanoparticles may be capable of detecting malignant cells (active targeting moiety), visualizing their location in the body (real-time *in vivo* imaging), killing the cancer cells with minimal side effects by sparing normal cells (active targeting and controlled drug release or photothermal ablation), and monitoring treatment effects in real time.

REFERENCES

1. McCarthy JR, Weissleder R. Multifunctional magnetic nanoparticles for targeted imaging and therapy. Adv Drug Deliv Rev 2008;60:1241-51.
2. Boisselier E, Astruc D. Gold nanoparticles in nanomedicine: Preparation, imaging, diagnostics, therapies and toxicity. Chem Soc Rev 2009;38:1759-82.
3. Xie J, Lee S, Chen X. Nanoparticle-based theranostic agents. Adv Drug Deliv Rev 2010;62:1064-79.
4. Praetorius NP, Mandal TK. Engineered nanoparticles in cancer therapy. Recent Pat Drug Deliv Formul 2007;1:37-51.
5. Kreuter J. Possibilities of using nanoparticles as carriers for drugs and vaccines. J Microencapsul 1988;5:115-27.
6. Portney GN, Ozkan M. Nano-oncology: Drug delivery, imaging, and sensing. Anal Bioanal Chem 2006;384:620-30.
7. Cai W, Hsu AR, Li ZB, Chen X. Are quantum dots ready for in vivo imaging in human subjects? Nanoscale Res Lett 2007;2:265-81.
8. Cai W, Shin DW, Chen K, Gheysens O, Cao Q, Wang SX, *et al*. Peptide-labeled near-infrared quantum dots for imaging tumor vasculature in living subjects. Nano Lett 2006;6:669-76.
9. Liu Z, Cai W, He L, Nakayama N, Chen K, Sun X, *et al*. In vivo biodistribution and highly efficient tumour targeting of carbon nanotubes in mice. Nat Nanotechnol 2007;2:47-52.
10. Thorek DL, Chen AK, Czupryna J, Tsourkas. supermagnetic iron oxide nanoparticles probes for molecular imaging. Ann Biomed Eng 2006,34:23-38.
11. Park JW, Benz CC, Martin FJ. Future directions of liposomeand immunoliposome-based cancer therapeutics. Semin Oncol 2004;31:196-205.
12. Huang X, Jain PK, El-Sayed IH, El-Sayed MA. Gold nanoparticles: Interesting optical properties and recent applications in cancer diagnostics and therapy. Nanomedicine (Lond) 2007;2:681-93.
13. Ferrari M. Cancer nanotechnology: Opportunities and challenges. Nat Rev Cancer 2005;5:161-71.
14. Grodzinski P, Silver M, Molnar LK. Nanotechnology for cancer diagnostics: Promises and challenges. Expert Rev Mol Diagn 2006;6:307-18.
15. Chai W, Gao T, Hong H, Sun J. Applications of gold nanoparticles in cancer nanotechnology. Nanotechnol Sci Appl 2008;1:17-32.
16. Salata OV. Application of nanoparticles in biology and medicine. J Nanobiotechnol 2004;2:3.
17. Mayavan S, Dutta NK, Choudhury NR, Kim M, Elvin CM, Hill AJ. Self-organization, interfacial interaction and photophysical properties of gold nanoparticle complexes derived from resilin-mimetic fluorescent protein rec1- resilin. Biomaterials 2011;32:2786-96.
18. Turkevich J, Stevenson PC, Hillier J. The nucleation and growth processes in the synthesis of colloidal gold. Discuss Faraday Soc 1951;11:55-75.
19. Hiramatsu H, Osterloh FE. A simple large-scale synthesis of nearly monodisperse gold and silver nanoparticles with adjustable sizes and with exchangeable surfactants. Chem Mater 2004;16:2509-11.
20. Weare WW, Reed SM, Warner MG, Hutchin J. Improved synthesis of small (dCORE ◎ 1.5 nm) phosphine-stabilized gold nanoparticles. J Am Chem Soc 2000;122:12890-1.
21. Manna A, Imae T, Aoi K, Okeda M, Yoga T Synthesis of dendrimer-passivated noble metal nanoparticles in a polar medium: Comparison of size between silver and gold particles. Chem Mater 2001;13:1674-81.
22. Kim YG, Oh SK, Crooks RM. Preparation and characterization of 1–2 nm dendrimer-encapsulated gold nanoparticles having very narrow size distributions. Chem Mater 2004;16:167-72.
23. Scott RW, Wilson OM, Crooks RM. Synthesis, characterization, and applications of dendrimer-encapsulated nanoparticles. J Phys Chem B 2005;109:692-704.
24. Anshup A, Venkataraman JS, Subramaniam C, Kumar RR, Priya S, Kumar TR, *et al*. Growth of gold nanoparticles in human cells. Langmuir 2005;21:11562-7.

25. Peleg G, Lewis A, Linial M, Loew LM. Nonlinear optical measurement of membrane potential around single molecules at selected cellular sites. Proc Natl Acad Sci U S A 1999;96:6700-4.
26. Cognet L, Tardin C, Boyer D, Choquet D, Tamarat P, Lounis B. Single metallic nanoparticle imaging for protein detection in cells. Proc Natl Acad Sci U S A 2003;100:11350-5.
27. Yang PH, Sun X, Chiu JF, Sun H, He QY. Transferrin-mediated gold nanoparticle cellular uptake. Bioconjug Chem 2005;16:494-6.
28. Loo C, Hirsch L, Lee MH, Chang E, West J, Halas N, *et al*. Gold nanoshell bioconjugates for molecular imaging in living cells. Opt Lett 2005;30:1012-4.
29. Dunn AR, Spudich JA. Dynamics of the unbound head during myosin V processive translocation. Nat Struct Mol Biol 2007;14: 246-8.
30. Sokolov K, Follen M, Aaron J, Pavlova I, Malpica A, Lotan R, *et al*. Real-time vital optical imaging of precancer using anti-epidermal growth factor receptor antibodies conjugated to gold nanoparticles. Cancer Res 2003;63:1999-2004.
31. Nitin N, Javier DJ, Roblyer DM, Richards-Kortum R. Widefield and high-resolution reflectance imaging of gold and silver nanospheres. J Biomed Opt 2007;12:051505.
32. Shi X, Wang S, Meshinchi S, Van Antwerp ME, Bi X, Lee I, *et al*. Dendrimer-entrapped gold nanoparticles as a platform for cancer-cell targeting and imaging. Small 2007;3:1245-52.
33. Durr NJ, Larson T, Smith DK, Korgel BA, Sokolov K, Ben-Yakar A. Two-photon luminescence imaging of cancer cells using molecularly targeted gold nanorods. Nano Lett 2007;7:941-5.
34. Li PC, Wei CW, Liao CK, Chen CD, Pao KC, Wang CR, *et al*. Photoacoustic imaging of multiple targets using gold nanorods. IEEE Trans Ultrason Ferroelectr Freq Control 2007;54:1642-7.
35. Thorek DL, Chen AK, Czupryna J, Tsourkas A. Superparamagnetic iron oxide nanoparticle probes for molecular imaging. Ann Biomed Eng 2006;34:23-38.
36. Su CH, Sheu HS, Lin CY, Huang CC, Lo YW, Pu YC, *et al*. Nanoshell magnetic resonance imaging contrast agents. J Am Chem Soc 2007;129:2139-46.
37. Sharma P, Brown SC, Bengtsson N, Zhang Q, Walter GA, Grobmyer SR, *et al*. Gold-speckled multimodal nanoparticles for noninvasive bioimaging. Chem Mater 2008;20:6087-94.
38. Laurent G, Félidj N, Truong SL, Aubard J, Lévi G, Krenn JR, *et al*. Imaging surface plasmon of gold nanoparticle arrays by far-field Raman scattering. Nano Lett 2005;5:253-8.
39. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cells assemble and align gold nanorods conjugated to antibodies to produce highly enhanced, sharp, and polarized surface Raman spectra: A potential cancer diagnostic marker. Nano Lett 2007;7:1591-7.
40. Qian X, Peng XH, Ansari DO, Yin-Goen Q, Chen GZ, Shin DM, *et al*. In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. Nat Biotechnol 2008;26:83-90.
41. Keren S, Zavaleta C, Cheng Z, de la Zerda A, Gheysens O, Gambhir SS. Noninvasive molecular imaging of small living subjects using Raman spectroscopy. Proc Natl Acad Sci U S A 2008;105:5844-9.
42. Copland JA, Eghtedari M, Popov VL, Kotov N, Mamedova N, Motamedi M, *et al*. Bioconjugated gold nanoparticles as a molecular based contrast agent: Implications for imaging of deep tumors using optoacoustic tomography. Mol Imaging Biol 2004;6:341-9.
43. Lilian EV, Mansoor MA. Multi-functional polymeric nanoparticles for tumour-targeted drug delivery. Expert Opin Drug Deliv 2006;3:205-16.
44. Ishida O, Maruyama K, Sasaki K, Iwatsuru M. Size-dependent extravasation and interstitial localization of polyethyleneglycol liposomes in solid tumor-bearing mice. Int J Pharm 1999;190:49-56.
45. Lasic DD. Applications of Liposomes. Handbook of Biological Physics. Vol. 1, Chap. 10. Elsevier Science B.V.; 1995.
46. Fries LF, Gordon DM, Richards RL, Egan JE, Hollingdale MR, Gross M, *et al*. Medical application of liposomes. Proc Natl Acad Sci U S A 1999;89:358-62.
47. Campos S. Liposomal anthracyclines: Adjuvant and neoadjuvant therapy for breast cancer Oncologist 2003;8:10-6.
48. Gopidas KR, Whitesell JK, Fox MA. Newkome-type Dendron-stabilized gold nanoparticles: Synthesis, reactivity, and stability. J Am Chem Soc 2003;125:6491-502.
49. Lin E, Nemunaitis J. Oncolytic viral therapies. Cancer Gene Ther 2001;11:643-64.
50. Kirn D, Martuza RL, Zwiebel J. Replication-selective virotherapy for cancer: Risk management and future directions. Nat Med 2001;7:781-7.
51. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res 2008;14:1310-6.
52. Manchester M, Singh P. Virus-based nanoparticles (Vnanoparticles): Platform technologies for diagnostic imaging. Adv Drug Deliv Rev 2006;58:1505-22.
53. Flenniken ML, Willits DA, Harmsen AL, Liepold LO, Harmsen AG, Young MJ, *et al*. Melanoma and lymphocyte cell-specific targeting incorporated into a heat shock protein cage architecture. Chem Biol 2006;13:161-70.
54. Bianco A, Kostarelos K, Partidos CD, Prato M. Biomedical applications of functionalised carbon nanotubes. Chem Commun (Camb) 2005;5:571-7.
55. Wu W, Wieckowski S, Pastorin G, Benincasa M, Klumpp C, Briand JP, *et al*. Targeted delivery of amphotericin B to cells by using functionalized carbon nanotubes. Angew Chem Int Ed Engl 2005;44:6358-62.
56. Pastorin G, Wu W, Wieckowski S, Briand JP, Kostarelos K, Prato M, *et al*. Double functionalisation of carbon nanotubes for multimodal drug delivery. Chem Commun (Camb) 2006;11:1182-4.
57. Wisse E, Braet F, Luo D, De Zanger R, Jans D, Crabbé E, *et al*. Structure and function of sinusoidal lining cells in the liver. Toxicol Pathol 1996;24:100-11.
58. Harris JM, Martin NE, Modi M. Pegylation: A novel process for modifying pharmacokinetics. Clin Pharmacokinet 2001;40:539-51.
59. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul 2001;41:189-207.
60. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene 2006;25:4633-46.
61. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: Role of ATP-dependent transporters. Nat Rev Cancer 2002;2:48-58.
62. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010;9:325-38.
63. Gold KA, Lee HY, Kim ES. Targeted therapies in squamous cell carcinoma of the head and neck. Cancer 2009;115:922-35.
64. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: A narrative literature review. Oral Oncol 2011;47:441-8.

Cite this article as: Sultana N, Shenoy SB, Sham ME, Keshav S, Kaul R. Nanogoldtechnology-imaging, sensing and target therapy in head and neck cancer. Clin Cancer Investig J 2012;1:6-12.

Source of Support: Nil, **Conflict of Interest:** None declared.