



"NANOTECHNOLOGY" THE NEW FATE OF THERAPY IN CANCER"

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ABSTRACT

The success of the nanotechnology has been led to the many innovative strategies for effective detection and treatment of tumor. The Multifunctional nanoparticles system can integrate imaging, targeting and treatment moieties on the surface and in the core, resulting in targeted delivery. One of the biggest dare associated with the treatment of tumor is the fact that current therapies for advance disease are not curative, necessitating treatment for many years and placing a significant health care burden on society. To reduce the burden of tumor, gold nanoparticles are more effective and targeted drug delivery system. The efficacy of chemotherapy is substantially limited by resistance of cancer cells to anticancer drug that fluctuates significantly in different patients. The essential purpose is to create a variety of drug delivery system to complement and further intensify the effectiveness of the available new medications. The perfect sustained release technology will provide a high level of safety with continuous release over an extended period of time while maintaining almost total drug bioactivity.

KEYWORDS: tumor, gold nanoparticles.

INTRODUCTION

Drug delivery by using the Nanomedicine has been increased from several decades. The nanotechnology creates unique structures has generated creative enthusiasm, and Brust of funding. Now a days nanotechnology has been increased in both patents and publications.^[1-2] Nanoparticle are particles of size having one dimension less than 100 nm. Example of nanoparticles for intravitreal drug delivery is ganciclovir and a formivirsen analog and tamoxifen loaded nanoparticles.^[3-4]

A fundamental change in chemotherapeutic research has taken place over a past decade, with the center of interest in moving from a discovery of new cytotoxic drugs to the development of target-specific protocols with the help of nanotechnology for the selective treatment of cancer.^[5] Multifunctional nanoparticles can also be loaded with imaging agents that helps to give diagnostic information during optical imaging, magnetic resonance and photothermal detection.^[6] The gold nanoparticles absorb the incident energy and to convert into heat that increase the temperature and dissipate by melting the cancerous cells by breaking the cell membrane.^[7]

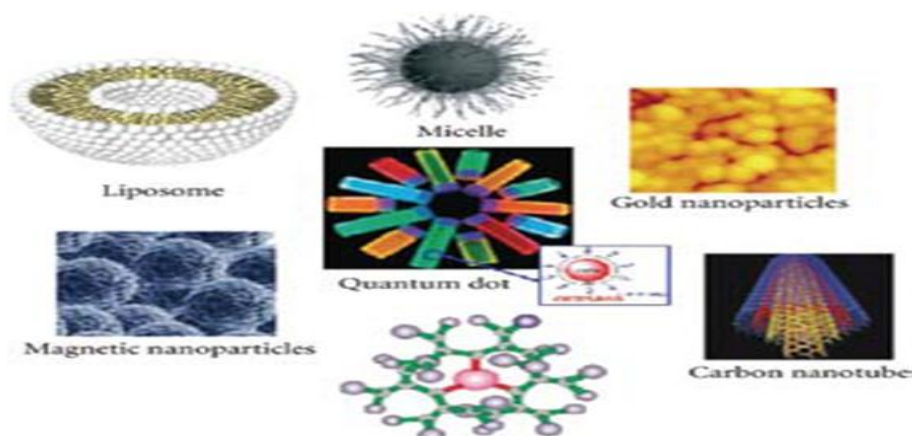


Figure 1: Examples of nanomaterials and nanocarrier systems (W. Cai et al.)^[8, 9]

Cancer is one of the world's most destructive disease having more than 10 million new cases every year.^[10] After better understanding of tumor biology and improvement in examination device and treatment of mortality has decreased in the past two years.^[11]

Nanotechnology and cancer detection

One of the major factors in successful treatment of cancer is to spot cancerous tumour cells in an early and perhaps curable stage. The unique physical and chemical properties of nanoparticles can develop synthetic scaffold that helps in imaging probes for detection and monitoring of cancer. The surface properties of nanoparticles are tunable, revealing injectible solutions of nanoparticles, revealing injectible solutions of nanoparticles, revealing injectible solutions of nanoparticles can be made without using organic solvents to attach water insoluble anticancer agents. Thus nanotechnology-based imaging techniques plays

important role in cancer research with their ability of highly sensitive probes for cancer detection.^[12]

The optical detection technique is used to detect presence of cancer and image cancer tissues with the help of functionalized nanomaterials where nanoparticle should either fluorescence or change their optical properties by fluorescence and UV-Vis absorption methods. When they bind to Cancer affected tissues such as silica nanoparticles doped with organic-based fluorescent dyes for detection of liver cell malignancy.^[13]

Nanomaterials used in synthesis of multifunctional nanoparticles

Organic and inorganic materials have been used to synthesize multifunctional nanoparticles having their own tectonic and suitable functionalities (Fig. 2) and they are estimated as impressive for drug delivery to tumors.^[14]

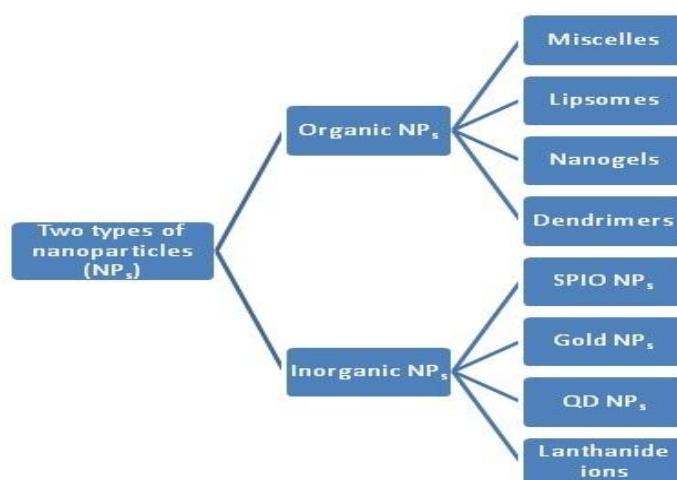


Figure:2 Inorganic and Organic nanoparticle (NP) material (NP), Multifunctional NP_s can be synthesized using two basic types of nanoparticles; Organic (micelles, Liposomes, nanogels and Dendrimers) and Inorganic Superparamagnetic iron oxide (SPIO), gold, quantum dots (QD) and Lanthanide ions.

Due to versatile surface and core chemistry, high degree of biodegradability, effective endocytosis by the target cell and high payload loading efficiency organic nanoparticles are used for synthesis of multifunctional nanoparticles.^[15]

Nanomicelles are formed by amphiphilic blocks the core made up of hydrophobic blocks such as propylene oxide, L-Lysine, aspartic acid, D, L-Lactic acid and spermine while the outermost region consists of hydrophilic blocks, such as poly (ethylene glycol) (PEG), Poly(N-vinyl-2-pyrrolidone) (PVP) and poly (vinyl alcohol).^[16]

Micellar nanoparticles can enclose hydrophobic drugs and imaging agents in their core, thus overcoming the need for toxic organic solvents. Liposomes are made from bilayers of enclosed spherical structures, such as phospholipids, cholesterol and other similar lipid molecules. Liposomes are perfect for the encapsulation

in their hydrophilic core of nucleic acid-based components to target tumor sites.^[17]

Polymeric nanogels are manufactured by cross-linking polymer chains to produce an inner porous space that can aid a large volume of payload and act as a promoter for delivery of multiple treatment mode.^[18]

Dendrimers have multiple functionalities at their terminal groups. Dendritic molecules such as polyamidoamines, Poly (propylene imine) polyamide, polyglycerol and triazine and synthesized by monomeric subunits.^[19]

Goldnanoparticles have optical and electrical properties that can be exploited in tumor imaging.^[20]

Goldnanoparticles and quantum dots have been prepared with organic polymers to form hybrid systems that can intact packaging of the drug and diagnostic strength for

efficacious drug delivery together with real-time monitoring of treatment response and tumor activity.^[21 - 22]

Lanthanide-doped nanoparticles are fluorescent nanoparticles that allow for the conversion of low energy light to high energy visible light eg. near infrared to UV emission. This upconversion is taken place by multiphoton absorptions or long lasting Luminescence of the lanthanides has been used in various cancer diagnostic trials.^[23 - 24]

Nanoscale diagnosis; molecular and cellular selection

The cancer progresses to an uncontrollable stage after onset as it is a heterogeneous disease.^[25-26] The chance of survival and quality of life of patients depends on the stage at which the disease has been detected. Thus the most important factor is to detect cancer cells as soon as possible. The conventional detection system consists of vacuum-assisted Mamotome Breast Biopsy system for breast cancer, Papanicolaou test for detection of pre-cancerous and cancerous processes for cervical cancer, Hemocult test for colorectal cancer, sputum cytology for lung cancer, digital rectal examination and prostate-specific antigen level for prostate cancer along with imaging i.e endoscopy, X-ray, CT, MRI and ultrasound. But, none of these are very sensitive for an early stage detection of cancerous cells.^[25 - 27]

Molecular biomarkers which is expressed during cancer onset can be detected by excitedly researched area of nanotechnology. Nanobiochips are the best examples that have been evolved as integrated biosensors using quantum dots that can be effectively used as multiplexed tools for quantitation of cancer markers such as carcinoembryonic antigen, cancer antigen 125 and Her-2/Neu (C-Erb B-2). They maintain very high speciality in serum and saliva and may also be integrated with nano fluidic arrays to facilitate detection of subcellular constituents.^[28- 29]

Early stage *In vivo* selection: For the early-stage detection of cancer onset, the transmuting events would be probed by non-invasive means. An example of this type of approach was reported by Harisinghani *et al.*^[30]

The authors exploited ferumox Tran-10 (Combidex; Advanced magnetic Inc, Cambridge, MA, USA), an ultra small, superparamagnetic, biodegradable iron oxide particle which is covered with a low-molecular-weight dextran as lymphotropic paramagnetic nanoparticles which facilitate spotting of clinically occult lymph-node metastases by enhancing MRI contrast in patients with prostate cancer. As metastases are undetectable by any other non-invasive approach. Further information on the onset and the status of the earlier stage disease can be obtained by probing the surrounding microenvironment by nanotechnology.^[31]

The formation of new blood vessels is one of the important signs of disease onset. The imaging of such type of sustained angiogenesis with very low amounts of epitope targeted by nanoparticles could be an important step for early stage detection of cancer.^[32]

Platform selection

There is no suitable platform to detect the measurable indicator of cancer at ultralow concentration, but hopeful results are emerging from nanotechnology-based approaches for the amplification and detection of such type of ultra-low signatures. Eg. nanoscale surface patterning. In nanoscale surface patterning carbon nanotube patterning has been used for the detection of carcinoembryonic antigen (CEA), a Glycosyl Phosphatidyl Inositol (GPI) cell surface-anchored glycoprotein involved during foetal development. The production of carcinoembryonic antigen stops before birth and its reappearance serves as an important cancer biomarker.^[33]

Ionization Time-of-Flight Mass spectrophotometry (SELDI-TOF-MS) /Surface-Enhanced Laser Desorption is MS Platform for the detection of trace amounts peptides and small molecules at the specific tumor microenvironment which is under study in combination with nanomaterials for early stage detection of cancer.^[34- 35]

Nanocarriers in cancer cell selection

A new mode of chemotherapeutic drug delivery is offered by nanocarriers. To develop such system the unique physiochemical properties of nanomaterials are used. Examples (i) tunable surface charge (+ve) to stimulate electrostatic interaction with comparatively negatively charged cancer cell surface. (Compared to normal cells) in order to stimulate endocytosis (ii) tunable hydrophilic surfaces having stealth properties to prevent clearance by reticuloendothelial system that prolong circulation times, thus preventing opsonisation, the process by which foreign particles are altered by opsonins to get efficiently engulfed by phagocytes (iii) modifications on the surface of nanoparticles to target specifically cancer cell membranes. By such type of approaches nanocarriers can deliver high concentrations of drug to a selected site with less systemic cytotoxicity. By incorporating on average a single antibody Herceptin, the antitumor efficacy of nanoparticles carrying the anticancer drug camptothecin.^[36]

Nanoscale cell selection

Passive selection: The physiology of tumor growth and progression is utilized for passive selection by nanoparticle system. The proliferation rate of cancer cell is faster than that of surrounding normal cells and thus control nutrients while generating more waste products, hence exerting stress on healthy cells. Healthy cells are replaced by cancer cells to form a small cluster of rapidly proliferating cells, until the tumor reaches the diffusion unit size of around 2 mm³.^[37]

Normal cells cannot compete for an adequate supply of amino acids, nutrients, oxygen and glucose. Normal cells are also unable to manage the excreted waste. By inducing angiogenesis and overcoming the stress by increasing the surrounding vascular, the cancer cells can survive. Defective angiogenesis cause abnormalities in the basement membrane of the vessels having gap size ranges from nanometer to micrometer scale. Also the normal diffusion of molecules prevented by abnormal lymphatic drainage network and asymmetric interstitial pressure.^[38]

This leaky vasculature helps nanomaterials to scape and become trapped within tumor due to dysfunctional lymphatic drainage system and leaky vasculature avoiding normal healthy tissue which has non-leaky vessels. Hence, nanotechnology based approaches utilize the opportunities to target tumor cells.^[31]

Due to the presence of sialic acids and overexpressed phospholipids negative charges are located on the surface of tumour endothelial cells which can be selected by positively charged nanoparticles due to electrostatic interactions.^[39]

Tissue specific cell selection

Breast cancer selection: Commercially Herceptin is used for the successful treatment of metastatic breast cancer. HER-2 is most important surface markers overexpressed in breast cancer.^[40]

Folate-receptor-mediated nanoparticle systems are developed in the case of prostate cancer. Luteinising hormone-releasing hormone receptor is important molecular marker on breast cancer cells for localized breast cancer selection. For the detection of breast cancer metastasis (LHRH-conjugated magnetic oxide nanoparticles) a superparamagnetic iron oxide nanoparticles (SPIONS) based system has been developed.^[41]

Nanomaterials: Intrinsic cell selection

Nanomaterials, which do not have any targeting molecules on the surface produce the cell specific response. Patra et al gave first report and showed that citrate-capped gold nanoparticles can selectively target human lung epithelial cells (A549) and do not interact with BHK21 kidney cells and hepG₂ Liver cells.^[42] Size, shape, charge and surface conjugations along with composition are the factors on which the intrinsic selection by nanoparticles are dependent. Different aspects of particles are reacted by different cell types. Sohaebuddin et al. showed that the mechanism of response of the particles, even using some nanomaterials, vary from one cell type to the next by using a set of Multiwall carbon nanotubes, silicon oxide and titanium oxide nanoparticles.^[43]

Novel functional nanomaterials for cancer therapy

The arrival of nanotechnology in cancer therapy, started when diagnostic, chemotherapeutic, antiangiogenesis and gene therapy agents (engineered oligonucleotides), were incorporated into nanosized particles or encapsulation within nanosized vesicles.^[44]

Sasisekaran et al published a report in Nature where his team developed “Nanocells” targeted to malignant tissues, is considered to be one of the most innovative multifunctional and intelligent drug delivery methods. The outer envelope of nanocell is absorbed by the tumor cell and released an anti-angiogenesis agent for shutdown of blood supply to the tumor and inner nanoparticles release chemotherapeutic agent. This synthetic view to cancer therapy also reduces the limitations of receiving decreased therapeutic concentration of chemotherapeutic agent by antiangiogenesis and the increased tumor invasiveness and resistance to chemotherapy caused by overexpression of (HIF1-alpha).^[45]

Most of the functional nanomaterials, which are nonradioactive in nature are used in hyperthermia. Composite metal nanoshells are one of the few earliest nanoshells for infrared hyperthermia. To provide optical resonance that can be systematically varied from near-UV to mid infrared by altering the dimensions of the nanoshells.^[46]

Upcoming multidisciplinary and supportive nanotechnologies for cancer therapy

Nanotechnology included with applied engineering and interdisciplinary innovation results in the development of small and low cost instruments for cancer treatment and diagnostics. Dr. otto zhou and his co-workers from the university of north Carolina capel Hill, are optimizing their new technology of carbon nanotube based X-ray machines are smaller in size, low in cost and provides clearer images and works at low temperature as compared to metallic filaments in conventional X-ray machines.^[47]

Gold nanoparticles

The synthesis of goldnanoparticles is much simpler and also pose minimal toxicity to kidney and liver where it accumulates after entering into systemic circulation compared to othernanoparticles.^[48-49]

Compared to normal human cells the nanogold has shown to have 600 times more absorption in cancer cells. El-sayed et al utilized the optical properties of nanogold to absorb and scatter light to demonstrate the detection and imaging og malignant cells. The cells were reported to be “shining” in dark field microscopy after the absorption of the nanogol-anti EGFR conjugate into the cancer cells.^[50]

REFERENCES

1. Wagner V, Dullaart A, Bock A-K, Zweck A. *Nat Biotechnol.* 2006; 24: 1211-1217.
2. Venditto VJ, & Szoka FC. Cancer Nanomedicines so many papers & so few drugs; *Advanced drug delivery reviews.* 2012; 09.038, 65(1): 80-88.
3. Rache JM, Merodio M, Arnedo A, et al. Albumin nanoparticles for the intravitreal delivery of anticytomegaloviral drugs. *Mini-Rev Med chem.* 2005; 293-305.
4. Dekozak Y, Andrieux K, Villarroya H, et al. Intraocular injection of tamoxifen-loaded nanoparticles; a new treatment of experimental autoimmune uveoretinitis. *Eur J Immunol.* 2004; 34: 3702-12.
5. Peer, D. et al, Nanocarriers as an emerging platform for cancer therapy. *Nature nanotechnology.* 2007; 2: 751-760.
6. Gindy, M. E.; Prud'homme, R. K. Multifunctional nanoparticles for imaging, delivery and targeting in cancer therapy. *Expert Opin. Drug Deliv.* 2009; 6: 865-878.
7. L. Tong, Y zhao, T. B. Huff, M. N. Hansen, A. Wei, J. X. Cheng, *Adv. Mater. Deerfield.* 2007; 19: 3136.
8. Cai W, chen X. Nanoplatforms for targeted molecular imaging in living subjects. *Small.* 2007; 3: 1840-1854.
9. Cai W, HSU AR, Z.-B. Li, Chen X. are quantum dots ready for invivo imaging in human subjects. *Nanoscale Res Lett.* 2007; 2: 265-281.
10. Stewart, B. W. & Kleihues, P. *World cancer report (World health organization Press, H Geneva).* 2003; 5: 255-268.
11. *Cancer Facts & Figures 2007 (American Cancer Society, Atlanta),* 2007.
12. Cuenca A.G., Jiang H., Hochwald S. N., Delano M., Cance W. G., Grobmyer S. R. Emerging Implications of nanotechnology on cancer diagnostics and therapeutics. *Cancer.* 2006; 107: 459-466.
13. He X, Duan J, Wang K, Tan W, Lin X, He C. A nobel fluorescent Label based on organic dye-doped silica nanoparticles for HepG liver cancer cell recognition. *J Nanosci Nanotechnol.* 2004; 4:6: 585-9.
14. Nazir S, Hussain. T, Ayub. A, Rashid. U, MacRobert A.J. *Nanomaterials in combating cancer: Therapeutic applications and developments.* *Nanomedicine.* 2014; 10: 19-34.
15. Jia, F, Liu, X, Li, L, Mallapragada, S, Narasimhan. B, Wang, Q. Multifunctional nanoparticles for targeted delivery of immune activating and cancer therapeutic agents. *J. Control Release.* 2013; 172: 1020-1034.
16. Felber, A.E. Dusfresne. M.H. Leroux, J.C. P^H-Sensitive vesicles, Polymeric micelles and nanospheres prepared with polycarboxylates. *Adv. Drug Del. Rev.* 2012; 64: 979-992.
17. Lin, Y, Y. kao, H. W, Li. J.J. Hwang, J. J; Tseng, Y.L. Lin, W.J.; Lin, M.H. Ting, G. Wang, H. E. Tumor burden talks in cancer treatment with pegylated liposomal drugs. 2013; 8: 63-78.
18. Chaeko. R. T, Ventura. J, Zhuang. J, Thayumanavan. S. *Polymernanogels; Nanoscopic drug delivery platform.* *Adv. Drug Deliv. Rev.* 2012; 64: 836-851.
19. Kojima. C, Kono. K, Maruyama. K, Takagishi. T. Synthesis of polyamidoamine dendrimers having poly (ethylene glycol) grafts and their ability to encapsulate anticancer drugs. *Bioconjug. Chem.* 2000; 11: 910-917.
20. Kim, D, Jon. S. Gold nanoparticles in image-guided Cancer therapy *Inorg. Chim. Acta.* 2012; 393: 154-164.
21. Bao, Q, Y. zhang, N. Geng, D.D. Xue, J, W. Merritt, M. Zhang, C Ding. Y. The enhanced longevity and liver targetability of paclitaxel by hybrid liposomes encapsulating paclitaxel-conjugated gold nanoparticles. *Int. J. Pharm.* 2014; 477: 408-415.
22. Liang, R.; Wang, J.; Wu, X.; Dong, L.; Deng, R.; Wang, K.; Sullivan, M.; S.; Wu, M.; Tao, J.; et al. Multifunctional biodegradable polymer nanoparticles with uniform sizes; Generation and invitro anti-melanoma activity. *Nanotechnology.* 2013; 24: 455-302.
23. Coll, J. L. Cancer optical imaging using fluorescent nanoparticles. *Nanomedicine.* 2011; 6: 7-10.
24. Naccache. R, Rodriguez. E, M. Bogdan, N. sanz-Rodriguez, F. Cruz Mdel, C. Fuente, A. J. Vetrone, F. Jaque, D. Sole, J.G. Capobianco J. A. High resolution fluorescence imaging of cancers using lanthanide ion-doped upconverting nanocrystals. *Cancers.* 2012; 4: 1067-1105.
25. Ferrari, M. Cancer nanotechnology: Opportunities and challenges. *Nature reviews cancer.* 2005; 5: 161-171.
26. Choi Y.E. *Nanotechnology for early cancer detection.* *Sensors.* 2010; 10: 428-455.
27. Tudos, A. J. et al. Trends in miniaturized total analysis systems for point-of-care testing in clinical chemistry. 2001; 1: 83-95.
28. Jokerst, J.V. et al. Nano-bio-chips for high Performance multiplexed Protein detection: determinations of cancer biomarkers in serum and saliva using quantum dot bioconjugate Labels. *Biosensors and Bioelectronics.* 2009; 24: 3622-3629.
29. Perfezou, M. et al. Cancer detection using nanoparticle-based Sensors. *Chemical Society Reviews.* 2012; 41: 2606-2622.
30. Harisinghani, M.G. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *New England Journal of Medicine.* 2003; 34: 2491-2499.
31. Liu, J. Multiplexed detection and characterization of rare tumor cells in hodgkin's lymphoma with multicolour quantum dots. *Analytical chemistry.* 2010; 82: 6237-6243.
32. Liu, P. Micro-CT Molecular Imaging of tumor Angiogenesis Using a Magnetite Nano-cluster

- Probe. *Journal of Biomedical Nanotechnology*, 2013; 9: 1041-1049.
33. Kwon, T. et al. Carbon Nanotube-Patterned surface-Based Recognition of carcinoembryonic Antigens in tumour cells for cancer Diagnosis. *The Journal of Physical chemistry Letters*. 2013; 4: 1126-1130.
34. Wulfkuhle, J.D. et al. Proteomic applications for the early detection of cancer. *Nature reviews cancer*. 2003; 3: 267-275.
35. Petricoin, E. F., & Liotta, L. A. SELDI-TOF-based serum proteomic pattern diagnostics for early detection of cancer. *Current opinion in Biotechnology*. 2004; 15(1): 24-30.
36. Han, H., & Davis, M.E. Single antibody, targeted nanoparticle delivery of camptothecin. *Molecular pharmaceuticals*, 2013; 10: 2558-2567.
37. Brannon-Peppas, L. & Blanchette, J.O. Nanoparticle and targeted systems for cancer therapy. *Advanced drug delivery reviews*. 2012; 56: 1649-1659.
38. Peer, D. Nanocarriers as an emerging platform for cancer therapy. *Nature of nanotechnology*. 2007; 2: 751-760.
39. Patra, H. K. & Dasgupta, A. K. Cancer cell response to nanoparticles: critically and optimality. *Nanomedicine: Nanotechnology, Biology and medicine*, 2012; 8: 842-852.
40. Baselga, J. et al. Recombinant humanized anti-HER2 antibody (Herceptin™) enhances the antitumour activity of Paclitaxel and Doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer research*. 1988; 58: 2825-2831.
41. Leuschner, C. et al. LHRH-Conjugated magnetic iron oxide nanoparticles for detection of breast cancer metastases. *Breast cancer research and treatment*. 2006; 99: 163-176.
42. Patra, H. K et al. Cell selective response to gold nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2007; 3: 111-119.
43. Sohaebuddin, S. K. et al. Nanomaterial cytotoxicity is composition, Size and cell type dependent. *Particle and fiber toxicology*, 2010; 7: 22-39.
44. Maksimenko A, Malvy C, Lambert G, Bertrand JR, Fattal E, Maccario J, et al. Oligonucleotides targeted against a junction oncogene are made efficient by nanotechnologies, *Pharm Res.*, 2003; 20: 1565-7.
45. Sengupta S, Eavarone D, Capila I, Zhao G, Watson N, Kiziltepe T, et al. Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system. *Nature*, 2005; 436: 568-72.
46. Loo C, Lin A, Hirsch L, Lee MH, Barton J, Halas N, et al. Nanoshell-enabled Photonics-based imaging and therapy of cancer. *Technol Cancer Res Treat*, 2004; 3: 33-40.
47. Pan Y, Xie H, Fedder GK. Endoscopic optical coherence tomography based on a microelectromechanical mirror. *Optics Letters*, 2001; 26: 1966-8.
48. Mathias BM, Walker M, Bethell D, Schiffrin DJ, Whyman R. synthesis of Thiol-derivatised Gold nanoparticles in a two-Phase Liquid-Liquid system. *J Chem Soc chem. Commun*, 1994; 801-2.
49. Hainfeld JF, Slatkin DN, Smilowitz HM. The use of Gold nanoparticles to enhance radiotherapy in mice. *Phys Med Biol*, 2004; 49: N309-15.
50. El-sayed IH, Huang X, El-sayed MA. Surface Plasmon resonance scattering and absorption of anti-EGFR antibody conjugated gold nanoparticles in cancer diagnostics: Applications in oral cancer *Nanolett*, 2005; 5: 829-34.