Universal Journal of Biomedical Engineering 2(3): 41-46, 2014 http://www.hrpub.org
DOI: 10.13189/ujbe.2014.020301

Gold Nano Particles (GNPs): An Emerging Solution of Cancer

Galib Hashmi, Masudul Haider Imtiaz*, Shahida Rafique

Department of Applied Physics, Electronics and Communication Engineering, University of Dhaka, Bangladesh
*Corresponding Author: masudul4145@gmail.com

Abstract Cancer, one of the leading causes that bring confirm death, is the subject of widespread fear and taboos. Although the complete elimination of cancer hasn't been discovered yet, "the war against cancer" has already been declared worldwide and research works are ongoing for cancer medicines. This paper presents a review on "Gold Nano Particle (GNP)", a magic bullet which might be the timely solution to bring win against cancer malignancy. GNPs can be used as cancer drug carriers, contrast agent or in target cancer therapy etc. Because cancer cell membrane has Nano size holes, the Nano structure of GNP would help it to enter the cancer cells. It has also the dissolving abilities, so no harm would be done to other parts of the body. By using near infrared LASER, localized heating of GNPs is also possible to destroy cancer cells. Test on rats using GNPs is found successful and the implementation on human is a matter of time. *In Vitro* and *In Vivo* observations on GNPs show much promises in near future.

Keywords Cancer, Gold Nano Particles (GNPs), In Vitro, In Vivo, Nanotechnology, Target Therapy

1. Introduction

According to GLOBOCAN database of International Agency for Research on Cancer (IARC), WHO, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compare to 12.7 and 7.6 million, respectively, in 2008 [1]. It is feared to raise the cancer cases to 22 million within next two decades. Major cancer deaths due to cancer in 2012 includes: lung cancer (1.59 million), liver (0.745 million), stomach (0.723 million), colorectal (0.649 million), breast (0.521 million) and esophageal cancer (0.40 million) [1]. Cancer is the sixth leading cause of death in Bangladesh; currently about 12 lakh cancer patients have been identified and every year around two lakh new people are being attacked by cancer and 1.5 lakh people die of it. IARC has assessed cancer-related death rate in Bangladesh was 7.5% in 2005 and projected to increase up to 13% by 2030 if immediate preventive and curative actions are not put into practice.

In 2013, WHO launched the Global Action Plan for the Prevention and Control of cancer [2], but still there has been no confirm solution how cancer can be cured. The National Cancer Institute (NCI) of US believes that nanotechnology could be the solution to cancer and has launched a plan of actions for achieving this great goal of harnessing power of nanotechnology to create a way to diagnose cancer and to locate and destroy these cancerous cells in the person's body with the help of nanotechnology [3]. Various nonorganic nanoparticles like Gold Nanoparticles (GNPs), SPIONs (Super Paramagnetic Iron Oxide Nanoparticles) and quantum dots (QDs) could be used as cancer Nano medicine. Of all nanoparticles, GNP hints the most promising future to cure cancer diseases because of its dissolve properties, small size, non-toxicity etc. Special magnetic characteristics are also found in GNPs which can be used to increase heat by MRI or X-Ray machine; those increased heat can be tooled to destroy cancer cells. *In Vitro* and *In Vivo* observations on GNPs are ongoing and significant result has been found. This paper reviews these special applications of GNPs in cancer treatments to have a clear insight of the futures of nanoparticle in medical treatment.

2. Background Study

(i) Overview of Cancer Treatment:

Cancer is a broad class of diseases characterized by out-of-control cell growth. Normal body cells grow, divide, and die in an orderly fashion and much faster in childhood. As the person grows adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue, called tumors. Tumors eventually grow and interfere with the digestive, nervous, and circulatory systems and release hormones that alter body function. Tumors also spread to other parts of the body through the blood and lymph, grow, invade and destroy other healthy tissues [4]. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat. The series of mutations that alters the behavior of cell individually is presented in Figure1 with a comparison with normal cell growth.

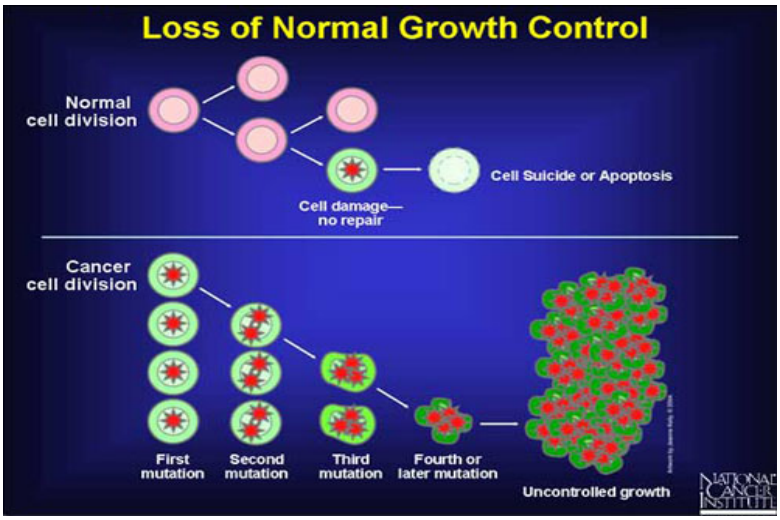

Figure 1. Comparison of abnormal cell division with normal healthy cells [5]

understood. The chances of surviving from this disease vary greatly by the type and location of the cancer and the extent of the disease at the start of treatment. Primary prevention, early detection, prompt diagnosis, appropriate treatment, and palliative care are the main strategies for cancer control. Treatment of cancer is complex, involving a range of therapies like surgery, radiotherapy, immunotherapy and chemotherapy (including hormonal manipulation) with psychological support. Still these therapies seek alternative because of some concerning side effects like infection, weight loss, fall in blood count, hair loss, nausea, vomiting, constipation, diarrhea, anemia, depression of the immune system etc. Having no target specificity, generic cancer drug not only kills cancer cells but also kills neighbor healthy cells; hence confirms toxicity. All these problems have led to the only solution *Nano Medicine*, the direct medical application of nanotechnology [6].

(ii) Concept of Nanotechnology:

Nanotechnology is not the simple technology of matters in reduced nanometer scale. Materials in the nanometer scale often exhibit some physical properties which is completely different from its bulk form. In US, nanotechnology has been defined as being "concerned with materials and systems whose structure and components exhibit novel and significantly improved physical, chemical and biological properties, phenomena and processes due to their Nano scale size" [7]. In general, nanotechnology deals with Nano materials, nanostructures and nanoparticles. Nano-materials are those which have structured component with at least one dimension less than 100 nm. A nanostructure is an atomic structure of Nano scale, size no longer than 100 nm. Particle satisfies this criterion is called nanoparticle. Nanoparticles' usages have already been explored; for instance, *Cerium Oxide nanoparticles* act as an antioxidant in traumatic injury. *Silicon Dioxide crystalline nanoparticles* are now being used to strengthening tennis racquets. *Carbon fibers*, *silver nanoparticles* have usage in fabric like killing bacteria, making clothing odor-resistant etc. *Iron nanoparticles* are commonly used to clean up carbon tetrachloride pollution in ground water. *Silicon nanoparticles* coating anodes of lithium-ion batteries can increase battery power and reduce recharge time etcetera. Nonorganic nanoparticles like *GNPs*, *SPIONs*, *QDs*, *Albumin bound paclitaxel* are proposed to be used as cancer Nano medicine. Of them, GNPs have exciting features to be the global cancer medicine.

3. Gold Nano Particles (GNPs)

GNPs are simply the nanoparticles of gold atoms [8]. In recent years there has been an explosion in GNP research in diverse fields including imaging, bioengineering and molecular biology [9]. The rapid increases in GNP publication graph (shown in Figure 2) testify this claim.

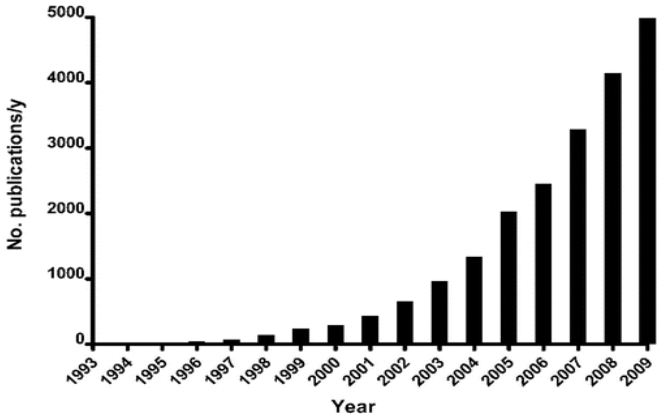

Figure 2. Year by Year Publications on Gold Nano Particles (Gnps) in Last Two Decades [10]

Synthesis of other metal nanoparticles may be achieved by reducing metal salts in organic solvents (like ethanol), but gold nanoparticles synthesis is different, by either:

1) Reduction of $HAuCl_4$ (Chloro-auric acid) in a solution of sodium citrate; further boiling in a wine-red

solution cause gold nanoparticles to form.

2) Mixing $HAuCl_4$in water to produce a solution that is subsequently transferred into toluene usingtetraoctylammonium bromide (TOAB), a phase transfer catalyst. Afterwards, the solution is stirred with sodium boro hydride, in the presence of certain alkanes which bind to the gold in the solution, allowing the formation of gold nanoparticles.

GNP in Cancer Treatment

Gold nanoparticles shows much promises as an agent for cancer therapy and has been researched thoroughly as drug carriers, contrast agents or in target therapy etc. Prospect of GNPs in cancer treatment with comparisons with alternates is discussed below.

3.1. Porous Cancer Cell Membrane

There are some marked difference between the outer coat or membrane of cancer cells and that of normal cells. The outer membrane of cancer cell is generally porous with holes of nano-meter range (Figure 3) [11]. But a normal cell does not have any pores. So nanometer GNPs can penetrate cancer cells easily and deliver carried cancer drugs. Whereas normal cells with no pore would remain unaffected.

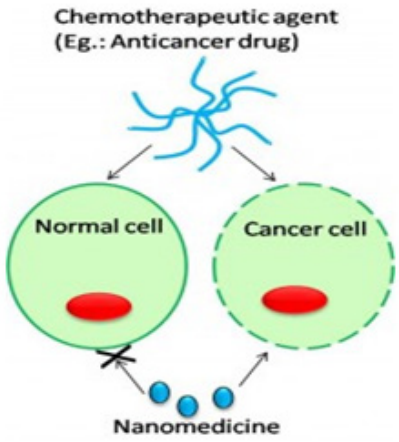

Figure 3. Delivery of Cancer Drugs to Porous Cancer Cell with Unaffected Nonporous Cells

3.2. Water Soluble GNPs

Gold is one of the few metals that are not rejected by our body unlike nickel, titanium [12]. Gold nanoparticles (AuNPs) thus provide non-toxic routes to drug and gene delivery applications. Researchers at the University of Trieste (Italy), The University of Bologna (Italy) and The University of Groningen (Netherlands) have successfully synthesized gold water soluble nanoparticle, protected by a thin layer of fluorinated amphiphillicthiols (sulphur-containing organic compound) that justify the claim [13].

3.3. GNP as Cancer Drug Carrier

Docetaxel, Doxorubicine, Paclitaxel etcetera well known cancer drugs, must be routed the cancer cells to destroy them. These drugs can be bonded covalently to GNPs and enable GNPs as drug carrier. Thus, GNP would act as a bus that carries passengers of cancer drugs. When the bus reaches the destination, passengers normally leave the bus. Similarly when GNPs reach the cancer cell, the drug would react with the cancer cells leaving GNPs behind. Example of such drug carrier GNP is *GNP-paclitaxel* [14], where two nm GNPs covalently functionalized with the chemotherapeutic drug, *paclitaxel*. The covalent bond of GNP with *paclitaxel* is done by a flexible hexa-ethylene glycol linker at the C-7 position of *paclitaxel* followed by phenol-terminated gold Nano crystals (shown in Figure 4). Paciotti et al. described that, coating of 26 nm *Au* particles with a mixture of tumor necrosis factor (TNF), polyethylene glycol and paclitaxel is capable of targeted drug delivery to solid tumors.

There are several techniques which is used to drug formulation and delivery, especially the production of nanosized drugs and pharmaceuticals. Mostly used technique is to penetrate a cell via passive diffusion across the lipid bilayer in a needle-like manner [15]. How much drug will be loaded that depends on the following equation:

$$\text{Drug Loading (\%)} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of nanoparticles}} \text{X } 100$$

The basic principle of dissolution rate (the mass of drug dissolved at a given time) was given by Noyes & Whitney (1897) and is described by the well-known equation:

$$\frac{dM}{dt} = \frac{DA}{h}(C_s - \text{C})$$

where ***dM/dt*** is the mass rate of dissolution, ***D*** is the diffusion coefficient of the drug in solution, ***A*** is the surface area of solid in contact with dissolution medium, $\boldsymbol{C_S}$ is the solubility of the drug, ***C*** is the concentration of the drug at time *t* and **h** is the thickness of the diffusion boundary layer at the solid's surface.

If a drug is encapsulated into Nano capsules, the drug has to traverse the capsule shell prior to reaching the surrounding medium. Release can occur by permeation through the capsule wall, erosion of the shell or diffusion through pores (if existing). The mass rate of permeation ***dM/dt*** of a drug through the capsule shell can be written according to the first law of Fick under sink condition:

$$\frac{dM}{dt} = \frac{DKAC_D}{h}$$

where ***D*** is the diffusion coefficient of the drug in the capsule shell, ***A*** is the surface area, ***K*** is the partitioning coefficient of the drug between capsule interior and shell, $\boldsymbol{C_D}$ is the solubility (solid) or concentration (dissolved) of the drug in the interior of the capsule and ***h*** is the thickness of the capsule shell.

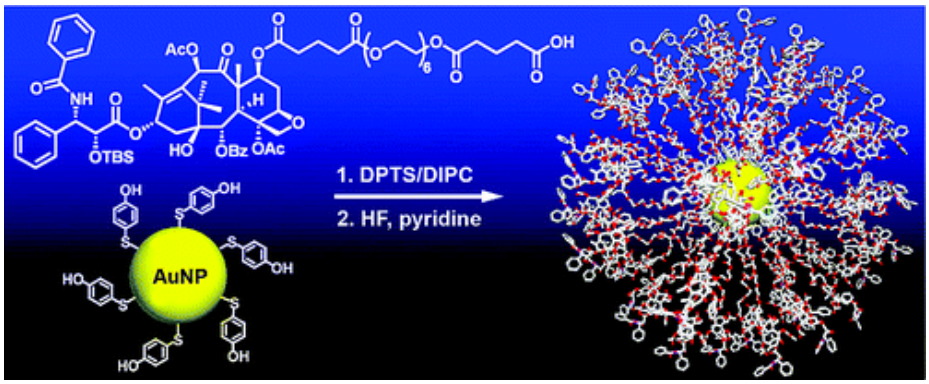

Figure 4. Illustration of GNP and paclitaxel covalent bond formation

3.4. GNP in Target Therapy

Generic drugs cause harmful side effects due to interaction with non-target tissues. But this problem can be mitigated using GNPs. GNPs provides targeted therapeutics (i.e. drug or gene delivery to specific locations for cancer treatment) [16].Receptor is a protein molecule usually found inside or on the surface of a cell, which receives chemical signals from outside the cell. GNPs could be bound to a receptor, and can cause some form of cellular/tissue responses (e.g. change in the electrical activity of the cell) which would block the growth and spread of cancer by interfering with cancer cells involved in tumor growth and progression (Figure 5).

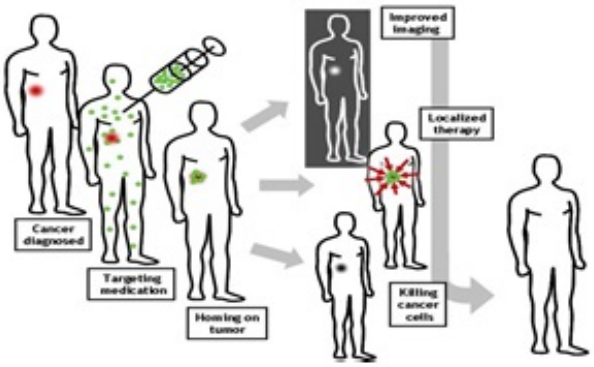

Figure 5. Illustration of Targeted GNP therapy [17]

3.5. Liposome GNPs

If any object is injected from the outside of human body, the defense mechanism inside the body shows resistance. But, lipid-lipid bilayer liposomes, generally created with two lipid layer, can avoid the attack of antibody when implanted. They are similar to normal cells in appearance, cover and structure; hence, body's defense mechanism cannot differentiate cells from liposome. GNPs, in drug delivery case, could be attached with liposome to avoid the attack of anti-body. Gold nanoparticles that successfully loaded into the bilayer of dipalmitoylphosphatidyl choline (DPPC) liposomes are stated as gold-loaded liposomes [18]. After targeting the cancer cell this drug will only damage the cancer cell, not the normal cell. The existence of gold nanoparticles in this DPPC bilayer is confirmed by transmission electron microscopy and energy dispersive X-ray spectrometers.

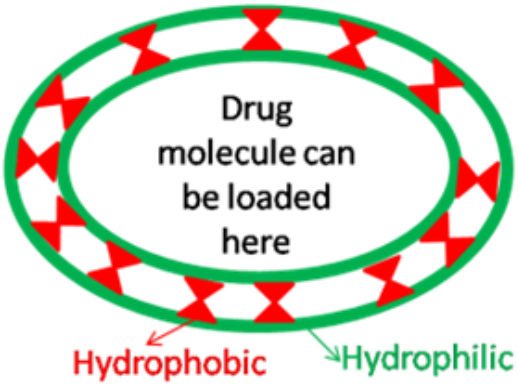

Figure 6. Structure of Liposome

3.6. No Vaccination by Injection

Fear of needles, also known as needle phobia, is the extreme fear of medical procedures like injections or hypodermic needles. Studies suggest that almost 5% of the population may be phobic of needles in general while children are more afraid of poking by injection. The Adult Dental Health Survey (UK) 1988 reported 8% of respondents with a fear of injections [19]. This needle problem can be solved by nanotechnology, especially with GNPs. GNPs or other nanoparticles can be taken orally or it can be rubbed into skin [20] for enabling nanoparticles to penetrate through skin and enter the blood stream. This procedure is also proved safer.

3.7. GNP Hyperthermia

Current Hyperthermic cancer therapies include applying heat to whole body altogether with cancer cells and other tissues, causing damage even to healthy tissues. Using gold nanoparticles this problem might be solved. Both *In vivo* (Latin of in life) experiment on a living subject and *In vitro* (in glass, outside of the organism in a test tube or petri dish) experiments have been carried out in this regard. After

completing the *In Vitro* studies, the researchers at Rice University under Prof. Jennifer West have demonstrated the use of 120 nm diameter Nano shells coated with gold to kill cancer tumors in mice. By conjugating antibodies or peptides to the Nano shell surface, Nano shells can be targeted to bond to cancerous cells. When the cancerous area is irradiated with a near-infrared LASER (of 808-852 nm), (Figure 7), it penetrates deep into the tissue without heating other muscles, only heating the nanoparticles to about 120^0Fahrenheit, results the destruction of targeted cancer cells [21] in around 30 days. This procedure has been justified by Dr. Dickson K. Kirui, Houston Methodist Research Institute [22].

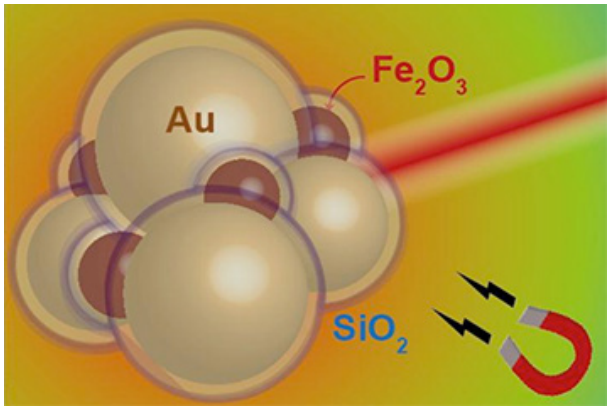

Figure 7. Near-infrared laser heating GNPs [23]

3.8. GNPs as Contrast Agents

A medical contrast medium (or contrast agent) is a substance used to enhance the visibility of internal body structures in medical imaging [24]. Several types of contrast media are in use in medical imaging, for instance, iodine and barium are using frequently for enhancing x-ray-based imaging methods. The properties of GNPs including small size, biocompatibility, high atomic number (high-Z) and the ability to bind targeting agents prove that they have potentials as contrast agents.

Mass attenuation coefficient is another important term defines the measurement of how strongly a chemical species or substance absorbs or scatters light at a given wavelength. It is seen that at energies above 80 KeV, the mass attenuation of gold is higher than that of iodine, suggesting that better contrast would be achieved with gold. For instance, at 100kV, the mass attenuation for gold is $5.16cm^2g^{-1}$, $1.94cm^2g^{-1}$ for iodine, $0.186cm^2g^{-1}$ for bones and $0.169cm^2g^{-1}$ for soft tissue. It is obvious gold provides 2.7 times more contrast per unit weight than iodine.

4. Limitations of GNPs

Regardless of many features of GNP as the solution to cancer, there are some marked limitations too. Though GNP promises greatly not to cause major harm human body, it is still unknown how much it will affect the body. Hence, GNP is still not tasted in human being and extensive *In Vivo* technique is yet to perform. There might be some side effects and scientists are not risking any human life without absolute confirmation. Again, GNP said to be rubbed into skin, but there are some other researchers who showed that it is not possible or if possible not much of the GNP will penetrate the skin [25].The major limitation of GNP is its high production cost and unavailability in the market. As scientists are not collaborating their initial findings and ideas with each other due to rigid terms and conditions of research organizations, GNP prospects like carrier drug, targeted therapy, liposome GNP all are getting invented in different lab considering different perspectives. Therefore, after satisfying all issues, it will take longer time to market GNP cancer drug at the cheaper rate.

5. Conclusions

Researches have confirmed that GNPs have many properties that are attractive for using in cancer therapy and have the ability to destroy cancer cells if properly applied. Still it can't be applied directly in cancer treatment unless the minimized cost factor is confirmed with increased effectiveness of cancer cure. State of art researches on GNPs are ongoing and will continue until the peak of success is reached. It is not too far that GNPs eradicates the cancer completely; the whole world is eagerly waiting for that glorious day.

REFERENCES

[1] Cancer statistics, GLOBOCAN database of International Agency for Research on Cancer (IARC), WHO. Available: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

[2] Cancer Fact Sheet, WHO. Available: http://www.who.int/mediacentre/factsheets/fs297/en/

[3] Cancer Research and Development, The National Cancer Institute (NCI) of US Available: http://nanogloss.com/nanotechnology/nanotechnology-cancer-research-and-development/

[4] What is cancer, NCI. Available: http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

[5] Photo courtesy Understanding Cancer Series: Cancer, National Cancer Institute (US.) Available: http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

[6] Robert A. Freitas Jr., Nanomedicine Volume I: Basic Capabilities (1999)

[7] Guozhong Cao, Nanostructures and Nanomaterials, Synthesis, Properties and Applications Imperial College Press (2006)

[8] Martina F Callaghan, Torben Lund, Parham Hashemzadeh, Ivan M Roitt and Richard H Bayford, "An investigation of the

impedanceproperties of gold nanoparticles", Journal of Physics: Conference Series, Volume 224 ,Number 1, 2010.

[9] S Jain, D G Hirst, and J M O'Sullivan, "Gold nanoparticles as novel agents for cancer therapy", The British Journal of Radiology, 85, pp 101(2012).

[10] ISI Web of Knowledge. Available from: www.webofknowledge.com

[11] DayanjaliWijesinghe , Mohan C. M. Arachchige, Andrew Lu, Yana K. Reshetnyak& Oleg A. Andreev, "pH dependent transfer of nano-pores into membrane of cancer cells to induce apoptosis", Scientific Reports 3,Article number: 3560, (2013).

[12] Jonathan Agbenyega,"Water soluble gold: Biomaterials",materials today, volume 11, number 12, (2008).

[13] Cristina Gentilini, Fabrizio Evangelista, Petra Rudolf, Paola Franchi, Marco Lucarini, and Lucia Pasquato, "Water-Soluble Gold Nanoparticles Protected by Fluorinated AmphiphilicThiolates", Journal of the American Chemical Society, Vol. 130, No. 46, 15678–15682, ASAP 10.1021/ ja8058364, (2008).

[14] J. D. Gibson , B.P. Khanal , and E. R. Zubarev, "Paclitaxel-Functionalized Gold Nanoparticles", Journal of the American Chemical Society, 129 (37), pp 11653, (2007).

[15] Melgardt M. de Villiers, PornanongAramwit and Glen S. Kwon, "Nanotechnology in Drug Delivery', Springer, AAPS Press, (2009).

[16] B. Panchapakesan, B. B.Newell, P. Sethu, M. Rao, and J. Irudayaraj, "Gold nanoprobes for theranostics",Nanomedicine, 6(10), pp 1787 (2011).

[17] Nahla S Barakat, Doaa A. Bin Taleb and Alia S Al Salehi, "Target Nanoparticles: An Appealing Drug Delivery Platform", Journal of Nanomedicine& Nanotechnology, S4, (2012).

[18] Park SH, Oh SG, Mun JY, and Han SS, "Loading of gold nanoparticles inside the DPPC bilayers of liposome and their effects on membrane fluidities", Colloids and Surfaces B: Biointerfaces 48(2), pp 112 (2006)

[19] Needle Phobia, Adult Dental Health Survey (UK). Available: http://www.dentalfearcentral.org/fears/needle-phobia/

[20] Francesca LareseFilon, MatteoCrosera, GianpieroAdami, Massimo Bovenzi, Federica Rossi, and Giovanni Maina, " Human skin penetration of gold nanoparticles through intact and damaged skin", Nanotoxicology, Early Online, 1–9, (2011).

[21] Loo C, Lin A, Hirsch L, Lee MH, Barton J, Halas N, West J, Drezek R., "Nanoshell-enabled photonics-based imaging and therapy of cancer." ,Technology in Cancer Research and Treatment, 3(1), pp 33 (2004).

[22] GNP destroys cancer cells, Cornell Chronicle, Cornell University. Available:http://www.news.cornell.edu/stories/2013/10/gold-plated-nano-bits-find-destroy-cancer-cells

[23] Georgios A. Sotiriou , Fabian Starsich , AthanasiaDasargyri , Moritz C. Wurnig , Frank Krumeich , Andreas Boss , Jean-Christophe Leroux , and Sotiris E. Pratsinis, "Photothermal Killing of Cancer Cells by the Controlled Plasmonic Coupling of Silica-Coated Au/Fe 2 O 3 Nanoaggregates", Advanced Functional Materials journal, Vol 24, Is19 pag 2818-2827, 2014.

[24] Edward H. Shortliffeand James J. Cimino, "Biomedical Informatics-Computer Applications in Health Care and Biomedicine", Springer, Fourth Edition,Chap-9,(2014).

[25] Adam C. Watkinson, Annette L. Bunge, Jonathan Hadgraft, and Majella E. Lane , "Nanoparticles Do Not Penetrate Human Skin—A Theoretical Perspective' , Pharmaceutical Research, Volume 30, Issue 8, pp 1943-1946, (2013).

[26] Sang Hyun Cho and Sunil Krishnan, Cancer Nanotechnology: Principles and Applications in Radiation Oncology CRC press, Taylor and Francis Group (2013).

[27] S Sonal, V Prabhakar, T Aneesh, and M Sabitha, "Nanomedicine: Promise of The Future In Disease Management", The Internet Journal of Nanotechnology. Volume 2 Number 2 (2007).

[28] W. F. Drew Bennett, Nicolas Sapay, and D. Peter Tieleman," Atomistic Simulations of Pore Formation and Closure in Lipid Bilayers", Biophysical Journal, Volume 106, pp-210–219, (2014).

[29] Jonathan Agbenyega, "Water soluble gold- Biomaterials", materials today, Volume 11, Number 12, (200