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GOLD NANOPRATICLES IN SCIENCE, TECHNOLOGY AND HEALTH CARE: A REVIEW

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ABSTRACT

The gold colloid is a solution of colloidal nanoparticles in gold in its liquid state. These particles are usually red in color. Due to their versatile properties in the field of optics, electronics, and molecular recognition, they are subjected to immense research. They are a preferred choice in technologies like electron microscopy, electronics, nanotechnology, material sciences, and health care. In many different types of colloidal gold synthesis, the combination of gold nanoparticles with certain ligands can increase its potent and usage in different fields. They are capable of delivering useful drugs in difficult areas like the brain, retina, tumors, and intracellular organelles. However, their efficiency highly depends on their size and shape. They are also under study as carriers for serious drugs like Paclitaxel. Gold nanoparticles are also used in drugs used for the treatment of cancer. However, if consumed in unprescribed amounts have proved to be toxic to the body. Different sizes of gold particles have shown buildup in parts of the brain, stomach, pancreas, kidneys, liver and blood. Gold nanorods have shown properties for being used as photothermal agent's in vivo applications. Gold nanoparticles are modified into nanorods, nanoshells, nanocages, etc. Gold nanoparticles are also used in on-site detection of harmful gases like H_2S.

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INTRODUCTION

Nanotechnology impacts substances in the range of 10^{-9} meters, including biotechnology, material sciences, computer sciences, medicines, pharmacy, and engineering [1]. Nanoparticles are available in two forms, namely crystalline and amorphous forms which have received demand all over the world for their beneficiary effects in fields of commercial applications, and thus have attracted many types of researches for studying its development and utility in various technologies [2-4]. Korea has devoted around trillions of their currency in the research of nanotechnology and has received high demands for creating research centers, with international facilities [5]. Many nanoparticles applications were developed which had created anticipation in different fields, which were related to the medical field in general, with fields of health care for their unique properties [1]. Nanotechnology came into existence in the 9th century, by the Mesopotamian people used for giving shine to their metal pots. In 1857, Michael Faraday discovered ruby gold nanoparticles (Au-NPs) which laid the foundation for new age nanotechnology [6-8]. 40 years later, Zsigmondy included his technology with that of Faradays and created 'seed-mediated method', which is still used today for the synthesis of various NPs. He also made an invention of ultra-microscope for differentiating the structure, size, shape of NPs [9, 10]. Svedberg, also invented ultracentrifuge, and showcased the motion of macromolecules was related to their shape and size [11-13]. At the same time in the past, G.Mie tried to experiment on the colors exhibited by gold (Au) colloids [14]. Also, the usage of Au-NPs increased into different biomedical fields, such as biosensors, clinical chemistry, immunoassays, genomics, photothermolysis of cancer cells, microorganism's prediction and control, drug delivery, optical imaging, and monitoring biological cells by the means of exploiting resonance scattering [15-24]. Biomedical has also adapted NPs in various processes. In the past few years, the main focus was on exploring their unknown properties and application in health care. Engineered NPs were used as a stage for the production of targeted drug delivery. Various researches on their physical, chemical, and optical properties were undertaken. Conjugates of these with several different drugs created curiosity towards their vast organic range of biological molecules, low toxic levels, and strong absorption [25-31]. Au-NPs played a major role in carrying drugs and vaccines to the required cells and tissues. The involvement of drugs with biomolecules was achieved by modifying Au-NPs. High concentrations of drugs with NPs were required to increase the effectiveness of the drug [32]. With the help of its physical and chemical properties, the release of drugs could be regulated [33-34]. Presently, the attention is placed on the structure of the divergent synthesis of Au-NPs, exemplary in nanospheres, nanorods, silica-coated Au nanoshells, nanocubes, nanorice, nanostars [35-38]. Beginning with the ancient Chinese medicines to the recent medicines, Au has been used primitively in health care. Au treats rheumatoid arthritis with a not yet know mechanism. Serious researches on Au-NPs are undertaken by scientists for studying its unique properties, low levels of toxicity and effects on the human system.

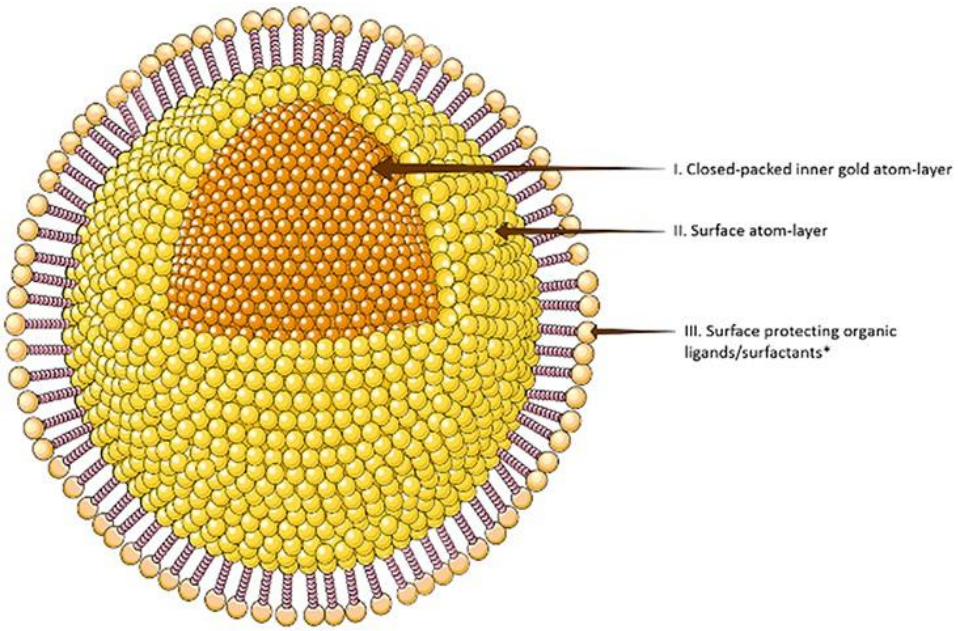

Figure 1: Structure of Gold Nano particles [92].

HISTORY

Michael Faraday was surprised to see the ruby color shown by the Au colloids. He was primarily focused on its interaction with light metal particles, but later developed interest in different factors like formation, properties, and nature of Au. The modern colloidal chemistry started from these studies, which led to further developments in nanoscience and nanotechnology. Faraday studied ruby glass from its use in the production of glass windows as a pigment. Since, the seventeenth century, Purple of Cassius was made by a combination of tin into Au which was then utilized in coloring glass and as paints [39]. He proved that Au-chloride undergoes reduction upon heating, with side reactions with several reagents, like organic compounds and phosphorus. Faraday highlighted the fact that metallic Au was dispersed evenly in ruby glass and fluids. When the particles are smaller than the wavelength of the incident light, the particles of different sizes show different colors rather than their real color [8]. Approximately 100 years later, the Ruby colored colloids were stabilized and their sizes were recorded to be in ranges between 2-6 nm as from an electron microscope.

Zsigmondy also developed an interest in colloids and began researching for the color and opacity of the ruby glass. As Faraday first produced Au colloids and other derivatives of ruby glass through reducing them, Zsigmondy found different sources to produce Au colloids. Later, an Au sol was considered as his major works. This important invention was the foundation for ultra-microscopy. Also, he determined the exact size of the particles and thus found several different and unique properties of these particles based on their sizes, motion with NPs. The light passage through hydrosol of Au could give an understanding of the motion of the particles. Therefore, Zsigmondy studied the changes in coloration of Au by adding citations, to obtain the effects from them. By the use of ultra-microscope, he proved that the reason for changes in colors can be attributed to the coagulated particles in various sizes and the action of protective agents that stop the coagulation. He developed useful machinery to perform ultrafiltration, for research on colloidal systems. Another scientist Theodor Svedberg also developed a curiosity in properties of colloidal sols, and hence he built an ultracentrifuge which could generate forces over 100,000 times of gravity. He developed his first low-speed ultracentrifuge and later a high-speed ultracentrifuge to find the shape and size of the protein particles. He also developed another way to find the molecular weight of proteins, with hemoglobin of about 67,000. Ostwald also played a key role in the synthesis of Au sols by experimental and theoretical ways. According to him, dipping your finger into the solution causes a reduction of organic substances present in the solution and in the skin, and the finger is thus stained bluish violet due to the formation of Au colloids [40-47].

NANOSPHERES

The alternative name for Au colloids is Au nanoparticles. The radius varies from 2 nm to 100 nm, which could be synthesized by reduction of aqueous HAuCl4 solution by adding various reducing agents in different quantities and conditions. The most commonly used reducing agent citrate is produced by monodisperse Au nanospheres [48, 49]. The amount of citrate was inversely proportional to the yield of nanospheres. The size could also be varied by modulating citrate and Au. The only disadvantage of this method was the low yield of Au nanospheres and the prohibited use of water as a solvent. Faraday in 1857, produced thermal stable Au nanospheres with a reduction in their dispersity by using the two-phase method of synthesis of nanospheres [50, 51]. The monodispersed nanospheres were produced by adding reactants at a faster rate in the cooling solution.

Therefore, there were many different methods for synthesizing nanospheres by adding reducing agents or ligands [52-54]. Also, dendrimers were utilized as a stabilizer in the synthesis of Au nanospheres [55-60]. The shape size of these nanospheres depended on factors like the concentration of reactant, HAuCl4, and blocked co-polymers. The absorption peaks of the nanospheres were about 510 nm to 550 nm. As their size increased, the absorption peak gained a longer wavelength. Several types of research tried to grow these nanospheres into human cells [61].

NANORODS

Many technologies were inspected for the synthesis of the Au nanorods. It was performed using the template method, based on the electrochemical deposition of Au in the pores of nonporous polycarbonate or alumina template membrane [62, 63]. Its diameter can be estimated by the diameter of the pores of the membrane. The length of the nanorod is controlled by the amount of deposition of Au in the membrane. Also, a major disadvantage of this technique is the low yield of Au nanorods, as only a single layer could be obtained. An electrochemical synthetic method for producing Au nanorods was recorded, where its length could be determined, which affects the ratio of long diameter over a shorter one [64-66]. The most commonly used method of synthesis of Au nanorods is the "Seed-mediated Synthesis", as it gave a higher ratio when compared with other methods [67, 68]. Au seed solution was also made in the presence of strong reducing agent NaBH4 for reducing Au chloride. This seed acts as a site for nucleation for the nanorods. By regulation of Au seed solution with respect to Au precursor, the ratio of Au nanorods could be controlled. Also, if $AgNO_3$ is added, it increases the yield of nanorods exponentially [69, 70].

NANOSHELLS

Nanoshells also mentioned as a type of spherical nanoparticle with dielectric core, with a layer of thin metallic shell mostly Au [71]. They include a quasi-particle, named Plasmon, manufactured from collective excitation of quantum plasma oscillation, where the electrons simultaneously oscillate with respect to all ions. This continuous oscillation referred to as Plasmon hybridization, is related to the hybridization of outer and inner shells, produces higher or lower energy levels. The lower level combines with the incident ray, while the higher level could not bind and become weak against the light. Therefore, the interactions of Plasmon hybridization on the thin shell layers would have more strength, and the shell thickness, overall particle radius, and all others combined together could find the wavelength of the incident light[72]. Due to the high reflective optical and chemical properties of the nanoshells, it is utilized in biomedical optical imaging, fluorescence enhancement of molecular emitters, in various therapies, surface enhancement, Raman spectroscopy, and surface-enhanced infrared absorption spectroscopy. Optical imaging uses interference from the deflected emitted light from a laser or an infrared source in studying their structure, texture, anatomic and chemical properties. In the near-infrared region between 700-900 nm, absorbance levels of bimolecular reached minimum level, giving a clear window for optical imaging [73]. Au nanoshells could also be processed by changing the composition and measurement of the layers, which could be made with Surface Plasmon Resonance (SPR) with peaks between visible and NIR regions [74]. By altering the core size ratio of its shell thickness, the SPR peak of Au nanoshells could be set for a required composition. By layering Au nanoshells with silica or polymer beads, Au nanoshells may be processed with SPR in the NIR regions [75]. The growth of silica cores was done by the reduction of Tetraethyl orthosilicate in ethanol, under the Stober process. A layer of Au solution by using the seed-mediated method was formed on the silica NPs. Other trials showcased the attachment process of small Au nanospheres to the core made of silica of diameter 2-4nm. Amino terminated saline was used until the seed particle integrated into one layer of the shell by the reduction of Au [76]. The diameter of the silica core could help calculate the diameter of the Au nanoshells.

Its thickness could be controlled by monitoring the amount of Au deposited on the core. Synthesis of Au nanoshells was performed by the Situ formation of Au nanoparticle from sensitive core-shell particles. The microgel can act as a core, which would diminish the particle aggregation and help in modulating the thickness of Au nanoshells from the plating of Au. We could produce cores with a relatively small radius, approximately 40 nm, with a narrow size distribution unlike silica [77].

NANOCAGES

In the year 2006, Au nanocages, made of controllable pores on its surface, synthesized in the galvanic replacement reaction of truncated silver nanocubes and aqueous HAuCl4 were produced. Also, it was noted that the generated morphology of the Silver nanostructures could be monitored by Pylol reduction. In Pylol reduction, ethylene glycol made $AgNo_3$ undergo reduction to produce silver atoms, and further reduction resulted in nanocrystals or seeds. Required nanostructures were obtained through the use of excessive silver atoms and by modulating the silver seed crystalline structure by polyvinylpyrrolidone, which had the potential of selective binding on the surface [78]. These nanostructures were used as a sacrificial template, used for the metamorphosis of Au into an internal hollow space through galvanic replacement [78, 79]. By adjustment in the molar ratios of silver to HAuCl4, the various dimensions including the thickness of the produced Au nanocages could be jurisdiction. Au nanocages showcased major advantages like:

i) Their surface Plasmon Resonance peaks could be altered by changing the ratios between Au nanocubes and HAuCl4. This could also complete the entire spectral region from 500 to 1200nm.

ii) It is controllable in the number of truncated corners and void size; their absorption coefficient could be changed.

iii) The Au nanocages could show the resonance peaks in the near IR region with a very small size.

iv) Surface specifications could be changed and thus could be used in different biomedical applications [79].

PHARMCACOKINECTIC AND BIO-DISTRIBUTION

Chemotherapeutic drugs including Au NPs, is highly effective in overcoming certain biological barriers that are removed by the help of nanoparticle design. In almost all kinds of drug delivery systems, clearance by RES is commonly used, happens due to opsonization and is reliable on its size, and can be circumvented via the AuNPs coating with hydrophilic polymer with a decrease in the size of the nanoparticles. Amplified angiogenesis, a trait of tumors, increases the fluid pressure, preventing the nanoparticles to affect the tumor interstitium. This shortcoming can be overcome by the utilization of passive accumulation of AuNPs by extravasation of leaky tumor vasculature. The site of action of the drug delivery is very important in nanoparticle drug delivery systems and is done by incorporating AuNPs with tumor-targeting ligands, and therapeutic molecules. In the process of designing AuNPs as a drug delivery vector, all the above-mentioned problems need to be overcome, by investigation of pharmacokinetic and different targeting strategies for different nanoparticle designs.

Generally, the size of a nanoparticle delivery system is between 10 to 100 nm. Within this range, there comes a range of pharmacokinetics and bio-distribution standards. There are many types of size-dependent blood half-life and bio-distribution specifications for spherical and rod-shaped AuNPs. De Jong and his co-workers detected AuNPs, in plasma mass spectrometry in the blood, liver, spleen, lung, kidney, testis, thymus, heart, brain after injecting 10,50,100 and 250 nm spherical AuNPs in male rats. Most amounts of AuNPs were detected in the blood, liver, and spleen and least in the lungs, kidney, testis, thymus, heart, and in the brain, after 24 hours passed from the time the injection was given. AuNPs of 10 nm worked mostly through every different organ, with the highest concentration in the liver and then in the spleen. After a day of the ejection, the percentage of dosage of Au was detected to be 46, 21, 44, and 31% in the liver for 10, 50,100, and 250 nm AuNPs respectively, in the spleen [80].

USES OF AuNPs IN CANCER

Standard methods for cancer treatment include surgery, chemotherapy, and radiation therapy. Utilizing their unique properties, most research of gold nanoparticles-based cancer treatment use photothermal therapy for targeting the cancer cells or tumor tissue, which is useful in the clinical trials. When radiation of focused laser pulses having a suitable wavelengths target, the gold nanospheres, nanorods, nanoshells and nanocages could kill the bacteria (Zharov et al) and cancer cells(Loo et al, Huang et al, Chen et al, Tong et al). It was estimated that a temperature of around 70-80°C could be obtained through light absorption by the gold nanoparticles (Huang et al) with about 150 antibodies conjugated to a nanoshell through a bifunctional PEG linker (Lowery et al). A common observation in this process is that it targets either EGFR or human epidermal growth factor receptor 2, mainly due to the availability of monoclonal antibodies (approved by the Food and Drug Administration for cancer therapy).

As the absorbance wavelength (in the visible region) of small gold nanospheres is not efficient in vivo application, the assembly of gold nanoclusters on the membrane of the cell was studied (Zharov et al). The study showed that the formation of nanoclusters resulted in increment in local absorption and red shifting when compared to cells without nanoclusters. Several advancements in laser-induced cancer cell killing were noted using a NIR laser. Gold nanoshells are comparatively larger (100-300nm in diameter) for SPR peaks in the NIR region. A similar study suggests that human breast cancer cells when incubated with gold nanoshells, undergo photo thermal-induced morbidity upon exposure to NIR light. In vivo testing, it was noted that exposure to NIR light in less amount to solid tumors treated with gold nanoshells gave a significant temperature increment, which was capable of producing irreversible tissue damage, while those not treated with gold nanoshells showed much lower temperature on exposure to NIR light and had no damage in the tissues[81].

APPLICATIONS OF AuNPs

Several reports suggest the versatility of AuNPs as a lifesaving drug delivery agent. The drug delivery system became very efficient in transferring the drug on the site without any safety issues. The most common routes being through the skin, nasal, mouth, ocular, rectal, buccal, and inhalation. Different biomolecules like proteins, antibodies, peptides, genes, and vaccinations also failed in delivering the drugs through the above-mentioned methods due to the organism's potential enzymatic degradation. These biomolecules were not absorbed in the circulation easily due to their molecular sizes. These could have been the major reasons for difficulty for protein and peptide-based drugs when it comes to delivering them with nanoneedle array. Thus, several different drugs were synthesized to increase the reproducibility, reliability, sensitivity, and specificity of the targeted areas. The following few methods are listed below.

A thin film drug delivery method rapidly dissolves hydrophilic polymer, which is easily absorbed when in contact with the buccal cavity. This self-micro emulsifying drug delivery system uses microemulsion for a special Ouzo effect. The neural drug delivery system targeted the specific injured nervous system. The acoustic targeted drug delivery is dependent on ultrasound for the transfer of energized molecules into the tissues. Drug delivery systems became a field of great study in nanomedicines. Thus, Au colloids became the preferred choice in the field of nanomedicines and drug delivery. The reason behind using AuNPs is to improve the targeted drug delivery, mainly in various cancer therapies. An excellent anticancer agent, Tumor necrosis factor-alpha (TNF- α) a cytokine, had toxic effects against cancer cells. A nanoparticle drug delivery system was formed with TNF- α combined with PEG-coated Au nanoparticle, which improved the damage to the tumor cells with a decreased toxicity from TNF- α [82-86]. From the above information, the combination of temperature and TNF- α PEG-coated Au nanoparticle enhanced the results when compared with TNF-α alone. TNF-α combined along with PEG-coated Au nanoparticle, given a proper dose and on time, prevents tumor growth. It also inhibited blood flow to the tumor cells thus, killing them by anti-angiogenesis approach. Even though the particles were monitored, no signs of accumulation in the organs were recorded. Another Au based formulation, named as CYT-6091, was created and distributed into the bloodstream, for delivering TNF-α into solid tumors9. Methotrexate (MTX), which inhibits dihydrofolate reductase, was used in chemotherapy for treating various types of cancer. A hybrid product of MTX-Au nanoparticle was produced to test its antitumor and toxic effects in vitro and in vivo. In a comprehensive study, MTX-Au hybrid inhibited tumor growth, with an equal amount of free MTX and no antitumor effect. Also, Au nanoshells with encapsulated horseradish peroxide (HRP) enzyme in the form of hydrogel in a hollow space were synthesized by soft chemical method for photothermal modulation of drug delivery. Au nanoshells permitted HRP to remain active in the hollow AuNPs. The intracellular uptake of AuNPs was found to be relying on their physical measurements, for example their size and shape, specifically when AuNPs were combined with ligands. Hence, this combination between the ligand and AuNPs had to be made stable and more reliable. As thiolated DNA strands could have been combined onto AuNPs via an Au-S bond, the femtosecond pulse excitation of AuNPs at 400nm wavelength could easily destroy the Au-S bond by an increment in the temperature of the particles absorbing the energy [87-91]

Objectives:

AuNPs are largely applicable in the health care sector. It is used in manufacturing of drugs used to treat carcinoma cells. It is considered to possess an essential drug delivery system. It is capable of delivering drugs at the most difficult of sites, which is often difficult by the other delivery systems like vaccinations.

CONCLUSION

The systemic review suggests that Au-NPS are an exclusive component in medical applications. The ease with which Au-NPS work provides it a huge platform in nanobiological products like oligonucleotides, antibodies, and proteins. Au colloids can be thoroughly dried and redispersed in any solution without any side-effects making them remarkable precursors for various functionalities. Au-NPs acts as an electrophile in the photoinduced electron transfer process. Au-NPs conjugated with ligands helps in controlling the reaction time, feed ratio, for various synergistic applications. Colloidal gold particles have widely been utilized in different fields. Au nanoparticles possess versatility and can be used in a broad range of applications, due to their electronic and physical properties and well-developed synthetic procedures. Many such features have made gold nanoparticles a preferred choice for various scientific researches, on nanomaterials. It also has various applications in health care and industrial products.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest

REFERENCE

1. Cai, W., et al. "Applications of gold nanoparticles in cancer nanotechnology. Nanotechnol Sci Appl 1: 17–32." (2008): 8.
2. Buzea, Cristina, Ivan I. Pacheco, and Kevin Robbie. "Nanomaterials and nanoparticles: sources and toxicity." Biointerphases 2.4 (2007): MR17-MR71.
3. Kawasaki, Ernest S., and Audrey Player. "Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer." Nanomedicine: Nanotechnology, Biology and Medicine 1.2 (2005): 101-109.

4. Horton, Michael A., and Abid Khan. "Medical nanotechnology in the UK: a perspective from the London Centre for Nanotechnology." Nanomedicine: Nanotechnology, biology and medicine 2.1 (2006): 42-48.
5. Thayer, Ann M. "Building up nanotech research." Chemical & engineering news 85.15 (2007): 15-21.
6. Sharma, Vivek, Kyoungweon Park, and Mohan Srinivasarao. "Colloidal dispersion of gold nanorods: Historical background, optical properties, seed-mediated synthesis, shape separation and self-assembly." Materials Science and Engineering: R: Reports 65.1-3 (2009): 1-38.
7. Thompson, David. "Michael Faraday's recognition of ruby gold: the birth of modern nanotechnology." Gold Bulletin 40.4 (2007): 267-269.
8. Xirouchaki, C., and R. E. Palmer. "Deposition of size-selected metal clusters generated by magnetron sputtering and gas condensation: a progress review." Philosophical Transactions of the Royal Society of London. Series A: Mathematical, Physical and Engineering Sciences 362.1814 (2004): 117-124.
9. Zsigmondy, Richard Adolf, and John Foote Norton. The chemistry of colloids. John Wiley & sons, Incorporated, 1917.
10. Zsigmondy, Richard. Colloids and the ultramicroscope: a manual of colloid chemistry and ultramicroscopy. J. Wiley & sons, 1909.
11. Svedberg, Theodor. The formation of colloids. J. & A. Churchill, 1921.
12. Svedberg, Theodor, and Arne Tiselius. Colloid chemistry. Vol. 16. Book department, The Chemical catalog company, inc., 1928.
13. Claesson, Stig, and Kai O. Pedersen. "The Svedberg, 1884-1971." (1972): 594-627.
14. Mie, Gustav. "Beiträge zur Optik trüber Medien, speziell kolloidaler Metallösungen." Annalen der physik 330.3 (1908): 377-445.
15. Stewart, Matthew E., et al. "Nanostructured plasmonic sensors." Chemical reviews 108.2 (2008): 494-521.
16. Baptista, Pedro, et al. "Gold nanoparticles for the development of clinical diagnosis methods." Analytical and bioanalytical chemistry 391.3 (2008): 943-950.
17. Gupta, Shalini, et al. "Characterization and optimization of gold nanoparticle-based silver-enhanced immunoassays." Analytical chemistry 79.10 (2007): 3810-3820.
18. Liu, Xiong, et al. "A one-step homogeneous immunoassay for cancer biomarker detection using gold nanoparticle probes coupled with dynamic light scattering." Journal of the American Chemical Society 130.9 (2008): 2780-2782.
19. Huang, Xiaohua, et al. "Plasmonic photothermal therapy (PPTT) using gold nanoparticles." Lasers in medical science 23.3 (2008): 217.
20. Lal, Surbhi, Susan E. Clare, and Naomi J. Halas. "Nanoshell-enabled photothermal cancer therapy: impending clinical impact." Accounts of chemical research 41.12 (2008): 1842-1851.
21. Luo, Pengju G., and Fred J. Stutzenberger. "Nanotechnology in the detection and control of microorganisms." Advances in applied microbiology 63 (2008): 145-181.
22. Han, Gang, Partha Ghosh, and Vincent M. Rotello. "Functionalized gold nanoparticles for drug delivery." (2007): 113-123.
23. Aaron, Jesse, et al. "Polarization microscopy with stellated gold nanoparticles for robust, in-situ monitoring of biomolecules." Optics express 16.3 (2008): 2153-2167.
24. Zharov, Vladimir P., et al. "In vivo photoacoustic flow cytometry for monitoring of circulating single cancer cells and contrast agents." Optics letters 31.24 (2006): 3623-3625.
25. Pissuwan, Dakrong, Takuro Niidome, and Michael B. Cortie. "The forthcoming applications of gold nanoparticles in drug and gene delivery systems." Journal of controlled release 149.1 (2011): 65-71.
26. Pissuwan, Dakrong, Stella M. Valenzuela, and Michael B. Cortie. "Therapeutic possibilities of plasmonically heated gold nanoparticles." TRENDS in Biotechnology 24.2 (2006): 62-67.
27. Hu, Min, et al. "Gold nanostructures: engineering their plasmonic properties for biomedical applications." Chemical Society Reviews 35.11 (2006): 1084-1094.
28. Daniel, Marie-Christine, and Didier Astruc. "Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology." Chemical reviews 104.1 (2004): 293-346.
29. Pissuwan, Dakrong, Stella M. Valenzuela, and Michael B. Cortie. "Prospects for gold nanorod particles in diagnostic and therapeutic applications." Biotechnology and Genetic Engineering Reviews 25.1 (2008): 93-112.
30. Tong, Ling, et al. "Gold nanorods as contrast agents for biological imaging: optical properties, surface conjugation and photothermal effects." Photochemistry and photobiology 85.1 (2009): 21-32.
31. Ghosh, Partha, et al. "Gold nanoparticles in delivery applications." Advanced drug delivery reviews 60.11 (2008): 1307-1315.
32. Chen, Po C., Sandra C. Mwakwari, and Adegboyega K. Oyelere. "Gold nanoparticles: from nanomedicine to nanosensing." Nanotechnology, science and applications 1 (2008): 45.
33. Skirtach, Andre G., et al. "Laser-induced release of encapsulated materials inside living cells." Angewandte Chemie International Edition 45.28 (2006): 4612-4617.
34. Sershen, S. R., et al. "Temperature-sensitive polymer–nanoshell composites for photothermally modulated drug delivery." Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 51.3 (2000): 293-298.
35. Sun, Yugang, and Younan Xia. "Shape-controlled synthesis of gold and silver nanoparticles." science 298.5601 (2002): 2176-2179.
36. Wang, Hui, et al. "Nanorice: a hybrid plasmonic nanostructure." Nano letters 6.4 (2006): 827-832.
37. Nehl, Colleen L., Hongwei Liao, and Jason H. Hafner. "Optical properties of star-shaped gold nanoparticles." Nano letters 6.4 (2006): 683-688.

38. Sun, Yugang, and Younan Xia. "Alloying and dealloying processes involved in the preparation of metal nanoshells through a galvanic replacement reaction." Nano Letters 3.11 (2003): 1569-1572.
39. Hunt, L. B. "The true story of Purple of Cassius." Gold Bulletin 9.4 (1976): 134-139.
40. Das, Minakshi, et al. "Review on gold nanoparticles and their applications." Toxicology and Environmental Health Sciences 3.4 (2011): 193-205.
41. Svedberg, The, and Robin Fåhraeus. "A new method for the determination of the molecular weight of the proteins." Journal of the American Chemical Society 48.2 (1926): 430-438.
42. Gray, George W. The ultracentrifuge. WH Freeman and Company, 1951.
43. Stokes, George Gabriel. On the effect of the internal friction of fluids on the motion of pendulums. Vol. 9. Cambridge: Pitt Press, 1851.
44. Adair, Gilbert Smithson. "A critical study of the direct method of measuring the osmotic pressure of hœmoglobin." Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character 108.748 (1925): 627-637.
45. Adair, Gilbert Smithson. "The osmotic pressure of haemoglobin in the absence of salts." Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character 109.750 (1925): 292-300.
46. Ostwald, Carl Wilhelm Wolfgang. An Introduction to Theoretical and Applied Colloid Chemistry," the World of Neglected Dimensions,". John Wiley & Sons, Incorporated, 1922.
47. Stern, Kurt H. "The Liesegang Phenomenon." Chemical Reviews 54.1 (1954): 79-99.
48. Frens, Gert. "Controlled nucleation for the regulation of the particle size in monodisperse gold suspensions." Nature physical science 241.105 (1973): 20-22.
49. Turkevich, John, Peter Cooper Stevenson, and James Hillier. "A study of the nucleation and growth processes in the synthesis of colloidal gold." Discussions of the Faraday Society 11 (1951): 55-75.
50. Giersig, Michael, and Paul Mulvaney. "Preparation of ordered colloid monolayers by electrophoretic deposition." Langmuir 9.12 (1993): 3408-3413.
51. Brust, Mathias, et al. "Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid–liquid system." Journal of the Chemical Society, Chemical Communications 7 (1994): 801-802.
52. Leff, Daniel V., Lutz Brandt, and James R. Heath. "Synthesis and characterization of hydrophobic, organically-soluble gold nanocrystals functionalized with primary amines." Langmuir 12.20 (1996): 4723-4730.
53. Weare, Walter W., et al. "Improved synthesis of small (d core≈ 1.5 nm) phosphine-stabilized gold nanoparticles." Journal of the American Chemical Society 122.51 (2000): 12890-12891.
54. Hiramatsu, Hiroki, and Frank E. Osterloh. "A simple large-scale synthesis of nearly monodisperse gold and silver nanoparticles with adjustable sizes and with exchangeable surfactants." Chemistry of Materials 16.13 (2004): 2509-2511.
55. Esumi, Kunio, et al. "Preparation of gold colloids with UV irradiation using dendrimers as stabilizer." Langmuir 14.12 (1998): 3157-3159.
56. Garcia, Maurie E., Lane A. Baker, and Richard M. Crooks. "Preparation and characterization of dendrimer− gold colloid nanocomposites." Analytical chemistry 71.1 (1999): 256-258.
57. Kim, Yong-Gu, Sang-Keun Oh, and Richard M. Crooks. "Preparation and characterization of 1− 2 nm dendrimer-encapsulated gold nanoparticles having very narrow size distributions." Chemistry of Materials 16.1 (2004): 167-172.
58. Manna, Abhijit, et al. "Synthesis of dendrimer-passivated noble metal nanoparticles in a polar medium: comparison of size between silver and gold particles." Chemistry of materials 13.5 (2001): 1674-1681.
59. Scott, Robert WJ, Orla M. Wilson, and Richard M. Crooks. "Synthesis, characterization, and applications of dendrimer-encapsulated nanoparticles." (2005): 692-704.
60. Shi, Xiangyang, et al. "Characterization of crystalline dendrimer-stabilized gold nanoparticles." Nanotechnology 17.4 (2006): 1072.
61. Anshup,†, et al. "Growth of gold nanoparticles in human cells." Langmuir 21.25 (2005): 11562-11567.
62. Martin, Charles R. "Nanomaterials: a membrane-based synthetic approach." Science 266.5193 (1994): 1961-1966.
63. Van der Zande, Bianca MI, et al. "Aqueous gold sols of rod-shaped particles." The Journal of Physical Chemistry B 101.6 (1997): 852-854.
64. Reetz, Manfred T., and Wolfgang Helbig. "Size-selective synthesis of nanostructured transition metal clusters." Journal of the American Chemical Society 116.16 (1994): 7401-7402.
65. Yu, Yu-Ying, et al. "Gold nanorods: electrochemical synthesis and optical properties." The Journal of Physical Chemistry B 101.34 (1997): 6661-6664.
66. Chang, Ser-Sing, et al. "The shape transition of gold nanorods." Langmuir 15.3 (1999): 701-709.
67. Jana, Nikhil R., Latha Gearheart, and Catherine J. Murphy. "Seed-mediated growth approach for shape-controlled synthesis of spheroidal and rod-like gold nanoparticles using a surfactant template." Advanced Materials 13.18 (2001): 1389-1393.
68. Busbee, Brantley D., Sherine O. Obare, and Catherine J. Murphy. "An improved synthesis of high-aspect-ratio gold nanorods." Advanced Materials 15.5 (2003): 414-416.
69. Jana, Nikhil R., Latha Gearheart, and Catherine J. Murphy. "Wet chemical synthesis of high aspect ratio cylindrical gold nanorods." The Journal of Physical Chemistry B 105.19 (2001): 4065-4067.
70. Jana, Nikhil R., et al. "Anisotropic chemical reactivity of gold spheroids and nanorods." Langmuir 18.3 (2002): 922-927.
71. Loo, Christopher, et al. "Nanoshell-enabled photonics-based imaging and therapy of cancer." Technology in cancer research & treatment 3.1 (2004): 33-40.

72. Brinson, Bruce E., et al. "Nanoshells made easy: improving Au layer growth on nanoparticle surfaces." Langmuir 24.24 (2008): 14166-14171.
73. Frangioni, John V. "In vivo near-infrared fluorescence imaging." Current opinion in chemical biology 7.5 (2003): 626-634.
74. Oldenburg, Steven J., et al. "Infrared extinction properties of gold nanoshells." Applied Physics Letters 75.19 (1999): 2897-2899.
75. Oldenburg, S. "1.; Averitt, RD; Westcott, SL; Halas, NJ." Chem. Phys. Lett 288 (1998).
76. Oldenburg, Steven J., et al. "Surface enhanced Raman scattering in the near infrared using metal nanoshell substrates." The Journal of chemical physics 111.10 (1999): 4729-4735.
77. Radloff, Corey, et al. "Metal nanoshell assembly on a virus bioscaffold." Nano letters 5.6 (2005): 1187-1191.
78. Chen, Jingyi, et al. "Facile synthesis of gold− silver nanocages with controllable pores on the surface." Journal of the American Chemical Society 128.46 (2006): 14776-14777.
79. Chen, Jingyi, et al. "Gold nanocages: bioconjugation and their potential use as optical imaging contrast agents." Nano letters 5.3 (2005): 473-477.
80. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3596176/?_escaped_fragment_=po=0.470219
81. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3596176/?_escaped_fragment_=po=0.470219
82. Mocellin, Simone, and Donato Nitti. "TNF and cancer: the two sides of the coin." Front Biosci 13.2774 (2008): 83.
83. Visaria, Rachana K., et al. "Enhancement of tumor thermal therapy using gold nanoparticle–assisted tumor necrosis factor-α delivery." Molecular cancer therapeutics 5.4 (2006): 1014-1020.
84. Paciotti, Giulio F., et al. "Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery." Drug delivery 11.3 (2004): 169-183.
85. Goel, Raghav, et al. "TNF-α–based accentuation in cryoinjury—Dose, delivery, and response." Molecular cancer therapeutics 6.7 (2007): 2039-2047.
86. Visaria, Rachana, et al. "Nanotherapeutics for enhancing thermal therapy of cancer." International Journal of Hyperthermia 23.6 (2007): 501-511.
87. Huennekens, F. M. "The methotrexate story: a paradigm for development of cancer chemotherapeutic agents." Advances in enzyme regulation 34 (1994): 397-419.
88. Chen, Yu-Hung, et al. "Methotrexate conjugated to gold nanoparticles inhibits tumor growth in a syngeneic lung tumor model." Molecular pharmaceutics 4.5 (2007): 713-722.
89. Sershen, S. R., et al. "Temperature-sensitive polymer–nanoshell composites for photothermally modulated drug delivery." Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 51.3 (2000): 293-298.
90. Chithrani, B. Devika, Arezou A. Ghazani, and Warren CW Chan. "Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells." Nano letters 6.4 (2006): 662-668.
91. Jain, Prashant K., Wei Qian, and Mostafa A. El-Sayed. "Ultrafast cooling of photoexcited electrons in gold nanoparticle− thiolated DNA conjugates involves the dissociation of the gold− thiol bond." Journal of the American Chemical Society 128.7 (2006): 2426-2433.
92. https://www.dovepress.com/cr_data/article_fulltext/s223000/223941/img/IJN_A_223941_O_F0003g.jpg