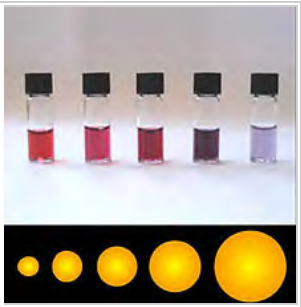
Colloidal gold

From Wikipedia, the free encyclopedia

Colloidal gold is a sol or colloidal suspension of nanoparticles of gold in a fluid, usually water. The liquid is usually either an intense red colour (for particles less than 100 nm) or blue/purple (for larger particles).[1][2] Due to the unique optical, electronic, and molecular-recognition properties of gold nanoparticles, they are the subject of substantial research, with applications in a wide variety of areas, including electron microscopy, electronics, nanotechnology,[3][4] and materials science.

The properties of colloidal gold nanoparticles, and thus their applications, depend strongly upon their size and shape.[5] For example, rodlike particles have both transverse and longitudinal absorption peak, and anisotropy of the shape affects their self-assembly.[6]



Suspensions of gold nanoparticles of various sizes. The size difference causes the difference in colors.

Contents

History

Known, or at least used (perhaps proceeding by accident without much understanding of the process) since ancient times, the synthesis of colloidal gold was crucial to the 4th-century Lycurgus Cup, which changes color depending on the location of light source.[7][8] Later it was used as a method of staining glass.


This cranberry glass bowl was made by adding a gold salt (probably gold chloride) to molten glass.

During the Middle Ages, soluble gold, a solution containing gold salt, had a reputation for its curative property for various diseases. In 1618, Francis Anthony, a philosopher and member of the medical profession, published a book called *Panacea Aurea, sive tractatus duo de ipsius Auro Potabili*[9] (Latin: gold potion, or two treatments of potable gold). The book introduces information on the formation of colloidal gold and its medical uses. About half a century later, English botanist Nicholas Culpepper published book in 1656, *Treatise of Aurum Potabile*,[10] solely discussing the medical uses of colloidal gold.

In 1676, Johann Kunckel, a German chemist, published a book on the manufacture of stained glass. In his book *Valuable Observations or Remarks About the Fixed and Volatile Salts-Auro and Argento Potabile, Spiritu Mundi and the Like*,[11] Kunckel assumed that the slight pink color of Aurum Potabile came from small particles of metallic gold, not visible to human eyes. In 1842, John Herschel invented a photographic process called chrysotype (from the Greek χρῡσός meaning "gold") that used colloidal gold to record images on paper.

Modern scientific evaluation of colloidal gold did not begin until Michael Faraday's work in the 1850s.[12][13] In 1856, in a basement laboratory of Royal Institution, Faraday accidentally created a ruby red solution while mounting pieces of gold leaf onto microscope slides.[14] Since he was already interested in the properties of light and matter, Faraday further investigated the optical properties of the colloidal gold. He prepared the first pure sample of colloidal gold, which he called 'activated gold', in 1857. He used phosphorus to reduce a solution of gold chloride. The colloidal gold Faraday made 150 years ago is still optically active. For a long time, the composition of the 'ruby' gold was unclear. Several chemists suspected it to be a gold tin compound, due to its preparation.[15][16] Faraday recognized that the color was actually due to the miniature size of the gold particles. He noted the light scattering properties of suspended gold microparticles, which is now called Faraday-Tyndall effect.[17]

In 1898, Richard Adolf Zsigmondy prepared the first colloidal gold in diluted solution.[18] Apart from Zsigmondy, Theodor Svedberg, who invented ultracentrifugation, and Gustav Mie, who provided the theory for scattering and absorption by spherical particles, were also interested in the synthesis and properties of colloidal gold.[6][19]

With advances in various analytical technologies in the 20th century, studies on gold nanoparticles has accelerated. Advanced microscopy methods, such as atomic force microscopy and electron microscopy, have contributed the most to nanoparticle research. Due to their comparably easy synthesis and high stability, various gold particles have been studied for their practical uses. Different types of gold nanoparticle are already used in many industries, such as medicine and electronics. For example, several FDA-approved nanoparticles are currently used in drug delivery.[20]

Physical properties

Optical

Colloidal gold has been used by artists for centuries because of the nanoparticle's interactions with visible light. Gold nanoparticles absorb and scatter light with incredible efficiency.[21] Ranging from vibrant reds to blues to black and finally to clear and colorless, colloidal gold has the ability to exhibit a wide range of colors depending on particle size, shape, local refractive index, and aggregation state. These colors occur because of a phenomenon called Localized Surface Plasmon Resonance (LSPR), in which conduction electrons on the surface of the nanoparticle oscillate in resonance with incident light.

Effect of size

As a general rule, the wavelength of light absorbed increases as a function of increasing nano particle size.[22] For example pseudo-spherical gold nanoparticles with diameters ~ 30 nm have a peak LSPR absorption at ~530 nm.[22]

Effect of local refractive index

Changes in the apparent color of a gold nanoparticle solution can also be caused by the environment in which the colloidal gold is suspended[23][24] The optical properties of gold nanoparticles depends on the refractive index near the nanoparticle surface, therefore both the molecules directly attached to the nanoparticle surface (i.e. nanoparticle ligands) and/or the nanoparticle solvent both may influence observed optical features.[23] As the refractive index near the gold surface increases, the NP LSPR will shift to longer wavelengths[24] In addition to solvent environment, the extinction peak can be tuned by coating the nanoparticles with non-conducting shells such as silica, bio molecules, or aluminium oxide.[25]

Effect of aggregation

When gold nano particles aggregate, the optical properties of the particle change, because the effective particle size, shape, and dielectric environment all change.[26]

Applications

Electron microscopy

Colloidal gold and various derivatives have long been among the most widely used labels for antigens in biological electron microscopy.[27][28][29][30][31] Colloidal gold particles can be attached to many traditional biological probes such as antibodies, lectins, superantigens, glycans, nucleic acids,[32] and receptors. Particles of different sizes are easily distinguishable in electron micrographs, allowing simultaneous multiple-labelling experiments.[33]

In addition to biological probes, gold nanoparticles can be transferred to various mineral substrates, such as mica, single crystal silicon, and atomically flat gold(III), to be observed under atomic force microscopy (AFM).[34]

Medical research

Drug delivery system

Gold nanoparticles can be used to optimize the biodistribution of drugs to diseased organs, tissues or cells, in order to improve and target drug delivery.[35][36] It is important to realize that the nanoparticle-mediated drug delivery is feasible only if the drug distribution is otherwise inadequate. These cases include drug targeting of difficult, unstable molecules (proteins, siRNA, DNA), delivery to the difficult sites (brain, retina, tumors, intracellular organelles) and drugs with serious side effects (e.g. anti-cancer agents). The performance of the nanoparticles depends on the size and surface functionalities in the particles. Also, the drug release and particle disintegration can vary depending on the system (e.g. biodegradable polymers sensitive to pH). An optimal nanodrug delivery system ensures that the active drug is available at the site of action for the correct time and duration, and their concentration should be above the minimal effective concentration (MEC) and below the minimal toxic concentration (MTC).[37]

Gold nanoparticles are being investigated as carriers for drugs such as Paclitaxel.[38] The administration of hydrophobic drugs require molecular encapsulation and it is found that nanosized particles are particularly efficient in evading the reticuloendothelial system.

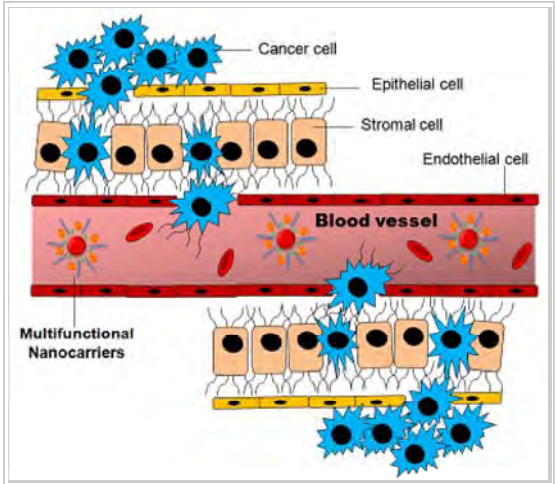
Gold nanoparticles are also used to circumvent multidrug resistance (MDR) mechanisms.[39] Mechanisms of MDR include decreased uptake of drugs, reduced intracellular drug concentration by activation of the efflux transporters, modifications in cellular pathways by altering cell cycle checkpoints, increased metabolism of drugs, induced emergency response genes to impair apoptotic pathways and altered DNA repair mechanisms.

Tumor detection

In cancer research, colloidal gold can be used to target tumors and provide detection using SERS (surface enhanced Raman spectroscopy) *in vivo*. These gold nanoparticles are surrounded with Raman reporters, which provide light emission that is over 200 times brighter than quantum dots. It was found that the Raman reporters were stabilized when the nanoparticles were encapsulated with a thiol-modified polyethylene glycol coat. This allows for compatibility and circulation *in vivo*. To specifically target tumor cells, the pegylated gold particles are conjugated with an antibody (or an antibody fragment such as scFv), against, e.g. epidermal growth factor receptor, which is sometimes overexpressed in cells of certain cancer types. Using SERS, these pegylated gold nanoparticles can then detect the location of the tumor.[40]

Gold nanoparticles accumulate in tumors, due to the leakiness of tumor vasculature, and can be used as contrast agents for enhanced imaging in a time-resolved optical tomography system using short-pulse lasers for skin cancer detection in mouse model. It is found that intravenously administrated spherical gold nanoparticles broadened the temporal profile of reflected optical signals and enhanced the contrast between surrounding normal tissue and tumors.[41]

Therefore, gold nanoparticles have the potential to join numerous therapeutic functions into a single platform, by targeting specific tumor cells, tissues and organs. Actually, Conde et al. reported the evaluation of the inflammatory response and therapeutic siRNA silencing via RGD-nanoparticles in a lung cancer mouse model. This study reported the use of siRNA/RGD gold nanoparticles capable of targeting tumor cells in two lung cancer xenograft mouse models, resulting in successful and significant *c-Myc* oncogene downregulation followed by tumor growth inhibition and prolonged survival of the animals. This delivery system can achieve translocation of siRNA duplexes directly into the tumour cell cytoplasm and accomplish successful silencing of an oncogene expression. Actually, RGD/siRNA-AuNPs can target preferentially and be taken up by tumor cells via integrin αvβ3-receptor-mediated endocytosis with no cytotoxicity, showing that can accumulate in tumor tissues overexpressing αvβ3 integrins and selectively delivered *c-Myc* siRNA to suppress tumor growth and angiogenesis.[42]



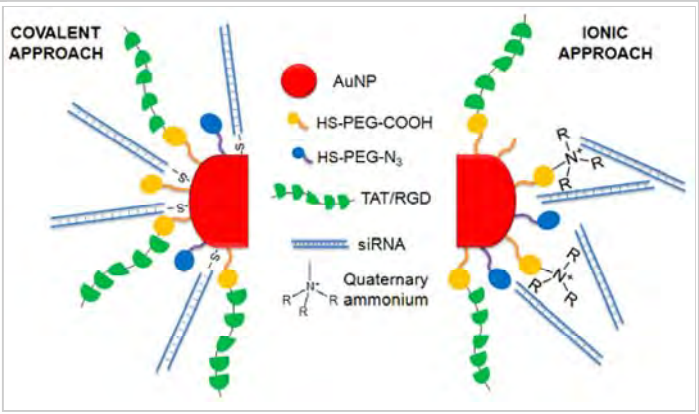
Tumor targeting via multifunctional nanocarriers. Cancer cells reduce adhesion to neighboring cells and migrate into the vasculature-rich stroma. Once at the vasculature, cells can freely enter the bloodstream. Once the tumor is directly connected to the main blood circulation system, multifunctional nanocarriers can interact directly with cancer cells and effectively target tumors.

Gene therapy

Gene therapy is receiving increasing attention and, in particular, small-interference RNA (siRNA) shows importance in novel molecular approaches in the knockdown of specific gene expression in cancerous cells. The major obstacle to clinical application is the uncertainty about how to deliver therapeutic siRNAs with maximal therapeutic impact. Gold nanoparticles have shown potential as intracellular delivery vehicles for siRNA oligonucleotides with maximal therapeutic impact.

Recently, Conde et al. provided evidence of *in vitro* and *in vivo* RNAi triggering via the synthesis of a library of novel multifunctional gold nanoparticles, using a hierarchical approach including three biological systems of increasing complexity: *in vitro* cultured human cells, *in vivo* freshwater polyp (*Hydra vulgaris*), and *in vivo* mice models. The authors developed effective conjugation strategies to combine, in a highly controlled way, specific biomolecules to the surface of gold nanoparticles such as: (a) biofunctional spacers: Poly(ethylene glycol) (PEG) spacers used to increase solubility and biocompatibility; (b) cell penetrating peptides such as TAT and RGD peptides: A novel class of membrane translocating agents named cell penetrating peptides (CPPs) that exploit more than one mechanism of endocytosis to overcome the lipophilic barrier of the cellular membranes and deliver large molecules and even small particles inside the cell for their biological actions; and (c) siRNA complementary to a master regulator gene, the protooncogene c-myc, were bond covalently (thiol-siRNA) and ionically (naked/unmodified siRNA) to gold nanoparticles.[43]

Gold nanoparticles have also shown potential as intracellular delivery vehicles for antisense oligonucleotides (ssDNA,dsDNA) by providing protection against intracellular nucleases and ease of functionalization for selective targeting.[44][45] Recently, Conde et al. developed a new theranostic system capable of intersecting all RNA pathways: from gene specific downregulation to silencing the silencers, i.e. siRNA and miRNA pathways. The authors reported the development gold nanoparticles functionalized with a fluorophore labeled hairpin-DNA, i.e. gold nanobeacons, capable of efficiently silencing single gene expression, exogenous siRNA and endogenous miRNAs while yielding a quantifiable fluorescence signal directly proportional to the level of silencing.[46] This method describes a gold nanoparticle-based nanobeacon as an innovative theranostic approach for detection and inhibition of sequence-specific DNA and RNA for *in vitro* and *ex vivo* applications. Under hairpin configuration, proximity to gold nanoparticles leads to fluorescence quenching; hybridization to a complementary target restores fluorescence emission due to the gold nanobeacons' conformational reorganization that causes the fluorophore and the gold nanoparticle to part from each other.[47] This concept can easily be extended and adapted to assist the in vitro evaluation of silencing potential of a given sequence to be later used for *ex vivo* gene silencing and RNAi approaches, with the ability to monitor real-time gene delivery action.[48]



Multifunctional siRNA-gold nanoparticles with several biomolecules: PEG, cell penetration and cell adhesion peptides and siRNA. Two different approaches were employed to conjugate the siRNA to the gold nanoparticle: (1) **Covalent approach**: use of thiolated siRNA for gold-thiol binding to the nanoparticle; (2) **Ionic approach**: interaction of the negatively charged siRNA to the modified surface of the AuNP through ionic interactions.

Photothermal agents

Gold nanorods are being investigated as photothermal agents for in-vivo applications. Gold nanorods are rod-shaped gold nanoparticles whose aspect ratios tune the surface plasmon resonance (SPR) band from the visible to near-infrared wavelength. The total extinction of light at the SPR is made up of both absorption and scattering. For the smaller axial diameter nanorods (~10 nm), absorption dominates, whereas for the larger axial diameter nanorods (>35 nm) scattering can dominate. As a consequence, for in-vivo applications, small diameter gold nanorods are being used as photothermal converters of near-infrared light due to their high absorption cross-sections.[49] Since near-infrared light transmits readily through human skin and tissue, these nanorods can be used as ablation components for cancer, and other targets. When coated with polymers, gold nanorods have been observed to circulate in-vivo with half-lives longer than 6 hours, bodily residence times around 72 hours, and little to no uptake in any internal organs except the liver.[50] Apart from rod-like gold nanoparticles, also spherical colloidal gold nanoparticles are recently used as markers in combination with photothermal single particle microscopy.

Radiotherapy dose enhancer

Following work by Hainfield et al.[51] there has been considerable interest in the use of gold and other heavy-atom containing nanoparticles to enhance the dose delivered to tumors. Since the gold nanoparticles are taken up by the tumors more than the nearby healthy tissue, the dose is selectively enhanced. The biological effectiveness of this type of therapy seems to be due to the local deposition of the radiation dose near the nanoparticles.[52] This mechanism is the same as occurs in heavy ion therapy.

Detection of toxic gas

Researchers have developed simple inexpensive methods for on-site detection of hydrogen sulfide H_2S present in air based on the antiaggregation of gold nanoparticles (AuNPs). Dissolving H_2S into a weak alkaline buff solution leads to the formation of HS-, which can stabilize AuNPs and ensure they maintain their red color allowing for visual detection of toxic levels of H_2S.[53]

Gold nanoparticle based biosensor

Gold nanoparticles are incorporated into biosensors to enhance its stability, sensitivity, and selectivity.[54] Nanoparticle properties such as small size, high surface-to-volume ratio, and high surface energy allow immobilization of large range of biomolecules. Gold nanoparticle, in particular, could also act as "electron wire" to transport electrons and its amplification effect on electromagnetic light allows it to function as signal amplifiers.[55][56] Main types of gold nanoparticle based biosensors are optical and electrochemical biosensor.

Optical biosensor

Gold nanoparticles improve the sensitivity of optical sensor by response to the change in local refractive index. The angle of the incidence light for surface plasmon resonance, an interaction between light wave and conducting electrons in metal, changes when other substances are bounded to the metal surface.[57][58] Because gold is very sensitive to its surroundings' dielectric constant,[59][60] binding of an analyte would significantly shift gold nanoparticle's SPR and therefore allow more sensitive detection. Gold nanoparticle could also amplify the SPR signal.[61] When the plasmon wave pass through the gold nanoparticle, the charge density in the wave and the electron I the gold interacted and resulted in higher energy response, so called electron coupling.[54] Since the analyte and bio-receptor now bind to the gold, it increases the apparent mass of the analyte and therefore amplified the signal.[54] These properties had been used to build DNA sensor with 1000-fold sensitive than without the Au NP.[62] Humidity senor was also built by altering the atom interspacing between molecules with humidity change, the interspacing change would also result in a change of the Au NP's LSPR.[63]

Electrochemical biosensor

Electrochemical sensor covert biological information into electrical signals that could be detected. The conductivity and biocompatibility of Au NP allow it to act as "electron wire".[54] It transfers electron between the electrode and the active site of the enzyme.[64] It could be accomplished in two ways: attach the Au NP to either the enzyme or the electrode. GNP-glucose oxidase monolayer electrode was constructed use these two methods.[65] The Au NP allowed more freedom in the enzyme's orientation and therefore more sensitive and stable detection. Au NP also acts as immobilization platform for the enzyme. Most biomolecules denatures or lose its activity when interacted with the electrode.[54] The biocompatibility and high surface energy of Au allow it to bind to a large amount of protein without altering its activity and results in a more sensitive sensor.[66][67] Moreover, Au NP also catalyzes biological reactions.[68][69] Gold nanoparticle under 2 nm has shown catalytic activity to the oxidation of styrene.[70]

Surface chemistry

In many different types of colloidal gold syntheses, the interface of the nanoparticles can display widely different character – ranging from an interface similar to a self-assembled monolayer to a disordered boundary with no repeating patterns.[71] Beyond the Au-Ligand interface, conjugation of the interfacial ligands with various functional moieties (from small organic molecules to polymers to DNA to RNA) afford colloidal gold much of its vast functionality.

Ligand exchange/functionalization

After initial nanoparticle synthesis, colloidal gold ligands are often exchanged with new ligands designed for specific applications. For example, Au NPs produced via the Turkevich-style (or Citrate Reduction) method are readily reacted via ligand exchange reactions, due to the relatively weak binding between the carboxyl groups and the surfaces of the NPs.[72] This ligand exchange can produce conjugation with a number of biomolecules from DNA to RNA to proteins to polymers (such as PEG) to increase biocompatibility and functionality. For example, ligands have been shown to enhance catalytic activity by mediating interactions between adsorbates and the active gold surfaces for specific oxygenation reactions.[73] Ligand exchange can also be used to promote phase transfer of the colloidal particles.[71] Ligand exchange is also possible with alkane thiol-arrested NPs produced from the Brust-type synthesis method, although higher temperatures are needed to promote the rate of the ligand detachment.[74][75] An alternative method for further functionalization is achieved through the conjugation of the ligands with other molecules, though this method can cause the colloidal stability of the Au NPs to breakdown.[76]

Ligand removal

In many cases, as in various high-temperature catalytic applications of Au, the removal of the capping ligands produces more desirable physicochemical properties.[77] The removal of ligands from colloidal gold while maintaining a relatively constant number of Au atoms per Au NP can be difficult due to the tendency for these bare clusters to aggregate. The removal of ligands is partially achievable by simply washing away all excess capping ligands, though this method is ineffective in removing all capping ligand. More often ligand removal achieved under high temperature or light ablation followed by washing. Alternatively, the ligands can be electrochemically etched off.[78]

Surface structure and chemical environment

The precise structure of the ligands on the surface of colloidal gold NPs impact the properties of the colloidal gold particles. Binding conformations and surface packing of the capping ligands at the surface of the colloidal gold NPs tend to differ greatly from bulk surface model adsorption, largely due to the high curvature observed at the nanoparticle surfaces.[71] Thiolate-gold interfaces at the nanoscale have been well-studied and the thiolate ligands are observed to pull Au atoms off of the surface of the particles to for “staple” motifs that have significant Thiyl-Au(0) character.[79][79][80] The citrate-gold surface, on the other hand, is relatively less-studied due to the vast number of binding conformations of the citrate to the curved gold surfaces. A study performed in 2014 identified that the most-preferred binding of the citrate involves two carboxylic acids and the hydroxyl group of the citrate binds three surface metal atoms.[81]

Toxicity

As gold nanoparticles (AuNPs) are further investigated for targeted drug delivery in humans, their toxicity needs to be considered. For the most part, it is suggested that AuNPs are biocompatible, but it is important to ask at what concentration they would be toxic, and if that concentration falls within the range of used concentrations. Toxicity can be tested *in vitro* and *in vivo*. *In vitro* toxicity results can vary depending on the type of the cellular growth media with different protein compositions, the method used to determine cellular toxicity (cell health, cell stress, how many cells are taken into a cell), and the capping ligands in solution.[82] *In vivo* assessments can determine the general health of an organism (abnormal behavior, weight loss, average life span) as well as tissue specific toxicology (kidney, liver, blood) and inflammation and oxidative responses.[82] *In vitro* experiments are more popular than *in vivo* experiments because *in vitro* experiments are more simplistic to perform than *in vivo* experiments.[82]

Toxicity and hazards in synthesis

While AuNPs themselves appear to have low or negligible toxicity, and the literature shows that the toxicity has much more to do with the ligands rather than the particles themselves, the synthesis of them involves chemicals that are hazardous. Sodium borohydride, a harsh reagent, is used to reduce the gold ions to gold metal. [83] The gold ions usually come from chloroauric acid, a potent acid.[84] Because of the high toxicity and hazard of reagents used to synthesize AuNPs, the need for more “green” methods of synthesis arose.

Toxicity due to capping ligands

Some of the capping ligands associated with AuNPs can be toxic while others are nontoxic. In gold nanorods (AuNRs), it has been shown that a strong cytotoxicity was associated with CTAB-stabilized AuNRs at low concentration, but it is thought that free CTAB was the culprit in toxicity .[85][86] Modifications that overcoat these AuNRs reduces this toxicity in human colon cancer cells (HT-29) by preventing CTAB molecules from desorbing from the AuNRs back into the solution.[85] Ligand toxicity can also be seen in AuNPs. Compared to the 90% toxicity of HAuCl4 at the same concentration, AuNPs with carboxylate termini were shown to be non-toxic.[87] Large AuNPs conjugated with biotin, cysteine, citrate, and glucose were not toxic in human leukemia cells (K562) for concentrations up to 0.25 M.[88] Also, citrate-capped gold nanospheres (AuNSs) have been proven to be compatible with human blood and did not cause platelet aggregation or an immune response.[89] However, citrate-capped gold nanoparticles sizes 8-37 nm were found to be lethally toxic for mice, causing shorter lifespans, severe sickness, loss of appetite and weight, hair discoloration, and damage to the liver, spleen, and lungs; gold nanoparticles accumulated in the spleen and liver after traveling a section of the immune system.[90] There are mixed-views for polyethylene glycol (PEG)-modified AuNPs. These AuNPs were found to be toxic in mouse liver by injection, causing cell death and minor inflammation.[91] However, AuNPs conjugated with PEG copolymers showed negligible toxicity towards human colon cells (Caco-2).[92] AuNP toxicity also depends on the overall charge of the ligands. In certain doses, AuNSs that have positively-charged ligands are toxic in monkey kidney cells (Cos-1), human red blood cells, and E. coli because of the AuNSs interaction with the negatively-charged cell membrane; AuNSs with negatively-charged ligands have been found to be nontoxic in these species.[87] In addition to the previously mentioned ‘‘in vivo’’ and ‘‘in vitro ’’ experiments, other similar experiments have been performed. Alkylthiolate-AuNPs with trimethlyammonium ligand termini mediate the translocation of DNA across mammalian cell membranes ‘‘in vitro’’ at a high level, which is detrimental to these cells.[93] Corneal haze in rabbits have been healed ‘‘in vivo’’ by using polyethylemnimine-capped gold nanoparticles that were transfected with a gene that promotes wound healing and inhibits corneal fibrosis.[94]

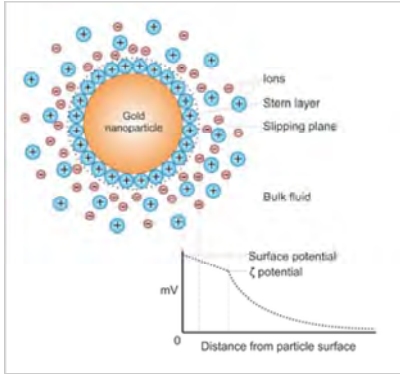
Toxicity due to size of nanoparticles

Toxicity in certain systems can also be dependent on the size of the nanoparticle. AuNSs size 1.4 nm were found to be toxic in human skin cancer cells (SK-Mel-28), human cervical cancer cells (HeLa), mouse fibroblast cells (L929), and mouse macrophages (J774A.1), while 0.8, 1.2, and 1.8 nm sized AuNSs were less toxic by a six-fold amount and 15 nm AuNSs were nontoxic.[95] There is some evidence for AuNP buildup after injection in ‘‘in vivo’’ studies, but this is very size dependent. 1.8 nm AuNPs were found to be almost totally trapped in the lungs of rats.[96] Different sized AuNPs were found to buildup in the blood,[97][98] brain,[97] stomach,[97] pancreas,[97] kidneys,[97] liver,[97][98] and spleen.[97][98]

Synthesis

Generally, gold nanoparticles are produced in a liquid ("liquid chemical methods") by reduction of chloroauric acid ($H[AuCl_4]$). After dissolving $H[AuCl_4]$, the solution is rapidly stirred while a reducing agent is added. This causes Au^{3+} ions to be reduced to Au^{+}ions. Then a disproportionation reaction occurs whereby 3 Au^{+} ions give rise to Au^{3+} and 2 Au^{0} atoms. The Au^{0} atoms act as center of nucleation around which further Au^{+} ions gets reduced. To prevent the particles from aggregating, some sort of stabilizing agent that sticks to the nanoparticle surface is usually added. In the Turkevich method of Au NP synthesis, citrate initially acts as the reducing agent and finally as the capping agent which stabilizes the Au NP through electrostatic interactions between the lone pair of electrons on the oxygen and the metal surface. Also, gold colloids can be synthesised without stabilizers by laser ablation in liquids.[99]

They can be functionalized with various organic ligands to create organic-inorganic hybrids with advanced functionality.[12]



Potential difference as a function of distance from particle surface.

Turkevich method

The method pioneered by J. Turkevich et al. in 1951 [100][101] and refined by G. Frens in the 1970s,[102][103] is the simplest one available. In general, it is used to produce modestly monodisperse spherical gold nanoparticles suspended in water of around 10–20 nm in diameter. Larger particles can be produced, but this comes at the cost of monodispersity and shape. It involves the reaction of small amounts of hot chloroauric acid with small amounts of sodium citrate solution. The colloidal gold will form because the citrate ions act as both a reducing agent and a capping agent. A capping agent is used in nanoparticle synthesis to stop particle growth and aggregation. A good capping agent has a high affinity for the new nuclei so it will bind to surface atoms which stabilizes the surface energy of the new nuclei and makes so that they cannot bind to other nuclei. [104]

Recently, the evolution of the spherical gold nanoparticles in the Turkevich reaction has been elucidated. It is interesting to note that extensive networks of gold nanowires are formed as a transient intermediate. These gold nanowires are responsible for the dark appearance of the reaction solution before it turns ruby-red.[105]

To produce larger particles, less sodium citrate should be added (possibly down to 0.05%, after which there simply would not be enough to reduce all the gold). The reduction in the amount of sodium citrate will reduce the amount of the citrate ions available for stabilizing the particles, and this will cause the small particles to aggregate into bigger ones (until the total surface area of all particles becomes small enough to be covered by the existing citrate ions).

Brust method

This method was discovered by Brust and Schiffrin in the early 1990s,[106] and can be used to produce gold nanoparticles in organic liquids that are normally not miscible with water (like toluene). It involves the reaction of a chloroauric acid solution with tetraoctylammonium bromide (TOAB) solution in toluene and sodium borohydride as an anti-coagulant and a reducing agent, respectively.

Here, the gold nanoparticles will be around 5–6 nm.[107] $NaBH_4$ is the reducing agent, and TOAB is both the phase transfer catalyst and the stabilizing agent.

It is important to note that TOAB does not bind to the gold nanoparticles particularly strongly, so the solution will aggregate gradually over the course of approximately two weeks. To prevent this, one can add a stronger binding agent, like a thiol (in particular, alkanethiols), which will bind to gold, producing a near-permanent solution.[108] [109] Alkanethiol protected gold nanoparticles can be precipitated and then redissolved. Thiols are better binding agents because there is a strong affinity for the gold-sulfur bonds that form when the two substances react with each other. [110] Tetra-dodecanthiol is a commonly used strong binding agent to synthesize smaller particles. [111] Some of the phase transfer agent may remain bound to the purified nanoparticles, this may affect physical properties such as solubility. In order to remove as much of this agent as possible, the nanoparticles must be further purified by soxhlet extraction.

Perrault method

This approach, discovered by Perrault and Chan in 2009,[112] uses hydroquinone to reduce $HAuCl_4$ in an aqueous solution that contains 15 nm gold nanoparticle seeds. This seed-based method of synthesis is similar to that used in photographic film development, in which silver grains within the film grow through addition of reduced silver onto their surface. Likewise, gold nanoparticles can act in conjunction with hydroquinone to catalyze reduction of ionic gold onto their surface. The presence of a stabilizer such as citrate results in controlled deposition of gold atoms onto the particles, and growth. Typically, the nanoparticle seeds are produced using the citrate method. The hydroquinone method complements that of Frens,[102][103] as it extends the range of monodispersed spherical particle sizes that can be produced. Whereas the Frens method is ideal for particles of 12–20 nm, the hydroquinone method can produce particles of at least 30–300 nm.

Martin method

This simple method, discovered by Martin and Eah in 2010,[113] generates nearly monodisperse "naked" gold nanoparticles in water. Precisely controlling the reduction stoichiometry by adjusting the ratio of $NaBH_4$-NaOH ions to $HAuCl_4$-HCl ions within the "sweet zone," along with heating, enables reproducible diameter tuning between 3–6 nm. The aqueous particles are colloidally stable due to their high charge from the excess ions in solution. These particles can be coated with various hydrophilic functionalities, or mixed with hydrophobic molecules for applications in non-polar solvents. In non-polar solvents the nanoparticles remain highly charged, and self-assemble on liquid droplets to form 2D monolayer films of monodisperse nanoparticles.

Nanotech applications

Bacillus licheniformis can be used in synthesis of gold nanocubes with sizes between 10 and 100 nanometres.[114] Gold nanoparticles are usually synthesized at high temperatures in organic solvents or using toxic reagents. The bacteria produce them in much milder conditions.

Navarro et al. method

The precise control of particle size with a low polydispersity of spherical gold nanoparticles remains difficult for particles larger than 30 nm. In order to provide maximum control on the NP structure, Navarro and co-workers used a modified Turkevitch-Frens procedure using sodium acetylacetonate (Na(acac) as the reducing agent and sodium citrate as the stabilizer.[115]

Sonolysis

Another method for the experimental generation of gold particles is by sonolysis. The first method of this type was invented by Baigent and Müller.[116] This work pioneered the use of ultrasound to provide the energy for the processes involved and allowed the creation of gold particles with a diameter of under 10 nm. In another method using ultrasound, the reaction of an aqueous solution of $HAuCl_4$ with glucose,[117] the reducing agents are hydroxyl radicals and sugar pyrolysis radicals (forming at the interfacial region between the collapsing cavities and the bulk water) and the morphology obtained is that of nanoribbons with width 30–50 nm and length of several micrometers. These ribbons are very flexible and can bend with angles larger than 90°. When glucose is replaced by cyclodextrin (a glucose oligomer), only spherical gold particles are obtained, suggesting that glucose is essential in directing the morphology toward a ribbon.

Block copolymer-mediated method

An economical, environmentally benign and fast synthesis methodology for gold nanoparticles using block copolymer has been developed by Sakai et al.[118] In this synthesis methodology, block copolymer plays the dual role of a reducing agent as well as a stabilizing agent. The formation of gold nanoparticles comprises three main steps: reduction of gold salt ion by block copolymers in the solution and formation of gold clusters, adsorption of block copolymers on gold clusters and further reduction of gold salt ions on the surfaces of these gold clusters for the growth of gold particles in steps, and finally its stabilization by block copolymers. But this method usually has a limited-yield (nanoparticle concentration), which does not increase with the increase in the gold salt concentration. Recently, Ray et al. demonstrated that the presence of an additional reductant (trisodium citrate) in 1:1 mole ratio with gold salt enhances the yield by manyfold at ambient conditions and room temperature.[119]

"Green chemistry" based methods

Methods employing phytochemicals

Phytochemicals found in various plant sources have been utilized as a means of developing a more economical and environmentally friendly synthetic pathway in the formation of gold nanoparticles. In accordance to the principles of "green chemistry," these methods employ the use of nontoxic chemicals, marginal energy consumption, renewable materials, and environmentally benign solvents to minimize the use, disposal, and health repercussions of hazardous chemicals.[120] Additionally, these methods provide a more efficient synthetic pathway through a one-step process without the use of supplementary

surfactants or polymers, capping agents, or templates to restrict agglomeration of the gold nanoparticles. This method is effective in producing well-defined gold nanoparticles since the phytochemicals perform a dual role as both a reducing agent of gold and as a stabilizer in the formation of a sturdy coating on the nanoparticles.[120] One "green" method that has been employed in the formation of gold nanoparticles utilizes the phytochemicals and polyphenols in Darjeeling black tea leaves, with water acting as a benign solvent at room temperature. The phytochemicals in the black tea reduce HAuCl4 and stabilize the aggregation of the gold atoms as the nanoparticle is formed. In addition to the "green" benefits of using black tea, the size of the nanoparticle is influenced by the concentration of the tea, and the absorbance and size of the gold nanoparticles formed can be easily determined using UV-Vis spectrometry abiding that an increase in λmax correlates to an increase in the size of the nanoparticle.[120][121]

Other "green" methods that have been studied and employed include the use of *Elettaria cardamomum* (cardamom) and cinnamon in the synthesis of gold nanoparticles, as well as *Syzygium aromaticum* (cloves) in the formation of copper nanoparticles and table sugar in the formation of silver nanoparticles.[122][123][124][125][126]

Gold nanoparticles as a benign starting material to access gold sponges

Besides using phytochemicals from plant sources to act as reducing agents and stabilizing agents, several other approaches have been taken to achieve more "green" approaches to gold nanoparticle syntheses. One such approach employs thiolated poly(ethylene glycol) (PEG Thiol) to destabilize gold nanoparticles prepared by citrate reduction so that they self-assemble into mesoporous gold sponges. Mesoporous gold sponges are attractive materials for molecular sensing by Surface-Enhanced Raman Spectroscopy (SERS), for catalysis, and for fuel cell construction. The following approach is "green" because PEG Thiol is biocompatible, and because it requires relatively little energy; PEG Thiol-triggered self-assembly of mesoporous gold sponges occurs at room temperature.[127] By contrast, the most popular method of generating mesoporous gold sponges, dealloying Au-Ag alloys, employs electrochemical corrosion.[128]

Gold nanoparticle synthesis in flow

Another green approach is a modification to the Turkevich citrate reduction making use of flow chemistry, reported by Bayazit et. al.[129] Flow chemistry is an appealing replacement for many heated batch reactions. By exposing more surface area of the reaction to the heating element, flow reactors heat a reaction faster and more evenly than can a batch reactor, promoting rapid nucleation and smaller particle sizes with higher monodispersity.

See also

- Colloidal silver
- Gold nanoparticles in chemotherapy

References

1. Bernhard Wessling, *Conductive Polymer / Solvent Systems: Solutions or Dispersions?*, **1996** (on-line here) (http://www.organic-nanometal.de/www2/Research/soludisp/solabstract.html)
2. University of Wisconsin–Madison: Making and conjugating colloidal metals (http://www.ansci.wisc.edu/facstaff/Faculty/pages/albrecht/albrecht_web/Program
3. Paul Mulvaney, University of Melbourne, *The beauty and elegance of Nanocrystals*, Use since Roman times (http://uninews.unimelb.edu.au/articleid_791.html)
4. C. N. Ramachandra Rao, Giridhar U. Kulkarni, P. John Thomasa, Peter P. Edwards, *Metal nanoparticles and their assemblies*, Chem. Soc. Rev., **2000**, 29, 27–35. (on-line here; mentions Cassius and Kunchel (http://pubs.rsc.org/ej/CS/2000/a904518j.pdf))
5. S.Zeng; Yong, Ken-Tye; Roy, Indrajit; Dinh, Xuan-Quyen; Yu, Xia; Luan, Feng; et al. (2011). "A review on functionalized gold nanoparticles for biosensing applications" (PDF). *Plasmonics*. **6** (3): 491–506. doi:10.1007/s11468-011-9228-1.
6. Sharma, Vivek; Park, Kyoungweon; Srinivasarao, Mohan (2009). "Colloidal dispersion of gold nanorods: Historical background, optical properties, seed-mediated synthesis, shape separation and self-assembly". *Material Science and Engineering Reports*. **65** (1–3): 1–38. doi:10.1016/j.mser.2009.02.002.
7. "The Lycurgus Cup". *British Museum*. Retrieved 2015-12-04.
8. Freestone, Ian; Meeks, Nigel; Sax, Margaret; Higgitt, Catherine. "The Lycurgus Cup — A Roman nanotechnology". *Gold Bulletin*. **40** (4): 270–277. doi:10.1007/BF03215599. ISSN 0017-1557.
9. Antonii, Francisci (1618). *Panacea aurea sive Tractatus duo de ipsius auro potabili*. Ex Bibliopolio Frobeniano.
10. Culpeper, Nicholas (1657). *Mr. Culpepper's Treatise of aurum potabile Being a description of the three-fold world, viz. elementary celestial intellectual containing the knowledge necessary to the study of hermetick philosophy. Faithfully written by him in his life-time, and since his death, published by his wife*. London.
11. Kunckel von Löwenstern, Johann (1678). *Utiles observationes sive animadversiones de salibus fixis et volatilibus, auro et argento potabili (etc.)*. Austria: Wilson.
12. V. R. Reddy, "Gold Nanoparticles: Synthesis and Applications" **2006**, 1791, and references therein
13. Michael Faraday, *Philosophical Transactions of the Royal Society*, London, 1857
14. "Michael Faraday's gold colloids | The Royal Institution: Science Lives Here". *www.rigb.org*. Retrieved 2015-12-04.
15. Gay-Lussac (1832). "Ueber den Cassius'schen Goldpurpur". *Annalen der Physik*. **101** (8): 629–630. Bibcode:1832AnP...101..629G. doi:10.1002/andp.18321010809.
16. Berzelius, J. J. (1831). "Ueber den Cassius' schen Goldpurpur". *Annalen der Physik*. **98** (6): 306–308. Bibcode:1831AnP....98..306B. doi:10.1002/andp.18310980613.
17. Faraday, M. (1857). "Experimental Relations of Gold (and Other Metals) to Light,". *Philosophical Transactions of the Royal Society*. **147**: 145. doi:10.1098/rstl.1857.0011.
18. Zsigmondy, Richard (December 11, 1926). "Properties of colloids" (PDF). Nobel Foundation. Retrieved 2009-01-23.
19. Zeng, Shuwen; Yu, Xia; Law, Wing-Cheung; Zhang, Yating; Hu, Rui; Dinh, Xuan-Quyen; Ho, Ho-Pui; Yong, Ken-Tye (2013). "Size dependence of Au NP-enhanced surface plasmon resonance based on differential phase measurement". *Sensors and Actuators B: Chemical*. **176**: 1128. doi:10.1016/j.snb.2012.09.073.
20. Hurst, Sarah J., ed. (2011-01-01). *Nanoparticle Therapeutics: FDA Approval, Clinical Trials, Regulatory Pathways, and Case Study - Springer*. Methods in Molecular Biology. Humana Press. doi:10.1007/978-1-61779-052-2_21. ISBN 978-1-61779-051-5.
21. Anderson, Michele L.; Morris, Catherine A.; Stroud, Rhonda M.; Merzbacher, Celia I.; Rolison, Debra R. (1999-02-01). "Colloidal Gold Aerogels: Preparation, Properties, and Characterization". *Langmuir*. **15** (3): 674–681. doi:10.1021/la980784i. ISSN 0743-7463.
22. Link, Stephan; El-Sayed, Mostafa A. (1999-05-01). "Size and Temperature Dependence of the Plasmon Absorption of Colloidal Gold Nanoparticles". *The Journal of Physical Chemistry B*. **103** (21): 4212–4217. doi:10.1021/jp984796o. ISSN 1520-6106.
23. Ghosh, Sujit Kumar; Nath, Sudip; Kundu, Subrata; Esumi, Kunio; Pal, Tarasankar (2004-09-01). "Solvent and Ligand Effects on the Localized Surface Plasmon Resonance (LSPR) of Gold Colloids". *The Journal of Physical Chemistry B*. **108** (37): 13963–13971. doi:10.1021/jp047021q. ISSN 1520-6106.
24. Underwood, Sylvia; Mulvaney, Paul (1994-10-01). "Effect of the Solution Refractive Index on the Color of Gold Colloids". *Langmuir*. **10** (10): 3427 –3430. doi:10.1021/la00022a011. ISSN 0743-7463.
25. Xing, Shuangxi; Tan, Li Huey; Yang, Miaoxin; Pan, Ming; Lv, Yunbo; Tang, Qinghu; Yang, Yanhui; Chen, Hongyu (2009-05-12). "Highly controlled core/shell structures: tunable conductive polymer shells on gold nanoparticles and nanochains". *Journal of Materials Chemistry*. **19** (20). doi:10.1039/b900993k. ISSN 1364-5501.

26. Ghosh, Sujit Kumar; Pal, Tarasankar (2007-11-01). "Interparticle Coupling Effect on the Surface Plasmon Resonance of Gold Nanoparticles: From Theory to Applications". *Chemical Reviews*. **107** (11): 4797–4862. doi:10.1021/cr0680282. ISSN 0009-2665.
27. "Colloidal gold, a useful marker for transmission and scanning electron microscopy" by M Horisberger and J Rosset *Journal of Histochemistry and Cytochemistry* Volume 25, Issue 4, pp. 295–305, 4 January 1977 [1] (http://www.jhc.org/cgi/content/abstract/25/4/295)
28. Electron Microscopy, 2nd Edition, by John J. Bozzola, Jones & Bartlett Publishers; 2 Sub edition (October 1998) ISBN 0-7637-0192-0
29. Practical Electron Microscopy: A Beginner's Illustrated Guide, by Elaine Evelyn Hunter. Cambridge University Press; 2nd edition (September 24, 1993) ISBN 0-521-38539-3
30. Electron Microscopy: Methods and Protocols (Methods in Molecular Biology), by John Kuo (Editor). Humana Press; 2nd edition (February 27, 2007) ISBN 1-58829-573-7
31. "Staphylococcal protein a bound to colloidal gold: A useful reagent to label antigen-antibody sites in electron microscopy", by Egidio L Romanoa and Mirtha Romanoa. *Immunochemistry* Volume 14, Issues 9–10, September –October 1977, pp. 711–715, doi:10.1016/0019-2791(77)90146-X (https://dx.doi.org/10.1016%2F0019-2791%2877%2990146-X)
32. Simultaneous visualization of chromosome bands and hybridization signal using colloidal-gold labeling in electron microscopy [2] (http://www.pnas.org/content/88/23/10916.abstract)
33. Double labeling with colloidal gold particles of different sizes (http://www.pnas.org/content/80/14/4339.abstract)
34. Grobelny, Jaroslaw, et al. "Size Measurement of Nanoparticles using Atomic Force Microscopy." Characterization of Nanoparticles Intended for Drug Delivery.Springer, 2011. 71–82. Print.
35. Han G, Ghosh P, Rotello VM. Functionalized gold nanoparticles for drug delivery. Nanomedicine (Lond) 2007;2:113–123.
36. Han G, Ghosh P, Rotello VM. Multi-functional gold nanoparticles for drug delivery. Adv Exp Med Biol 2007;620:48–56.
37. Langer R. Biomaterials in drug delivery and tissue engineering: one laboratory's experience. Acc Chem Res 2000;33:94–101.
38. *Paclitaxel-Functionalized Gold Nanoparticles* Jacob D. Gibson, Bishnu P. Khanal, and Eugene R. Zubarev J. Am. Chem. Soc. **2007**, 129, 11653–11661 doi:10.1021/ja075181k (https://dx.doi.org/10.1021%2Fja075181k)
39. Conde, J.; de la Fuente, JM; Baptista, PV. "Nanomaterials for reversion of multidrug resistance in cancer: a new hope for an old idea? (http://www.frontiersin.org/Journal/10.3389/fphar.2013.00134/full)." Front. Pharmacol.2013. Vol 4 No 134.
40. Qian, Ximei. *In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags.* Nature Biotechnology. 2008. Vol 26 No 1.
41. Sajjadi AY, Suratkar AA, Mitra KK, Grace MS. *Short-Pulse Laser-Based System for Detection of Tumors: Administration of Gold Nanoparticles Enhances Contrast*. J. Nanotechnol. Eng. Med.. 2012;3(2):021002-021002-6. doi:10.1115/1.4007245.
42. Conde J, Tian F, Hernández Y, Bao C, Cui D, Janssen KP, Ibarra MR, Baptista PV, Stoeger T, de la Fuente JM. *In vivo tumor targeting via nanoparticle-mediated therapeutic siRNA coupled to inflammatory response in lung cancer mouse models.* Biomaterials. 2013;34(31):7744–53. doi: 10.1016/j.biomaterials.2013.06.041.
43. Conde J, Ambrosone A, Sanz V, Hernandez Y, Marchesano V, Tian F, Child H, Berry CC, Ibarra MR, Baptista PV, Tortiglione C, de la Fuente JM. *Design of multifunctional gold nanoparticles for in vitro and in vivo gene silencing.* ACS Nano. 2012;6(9):8316–24. doi: 10.1021/nn3030223.
44. Conde J, de la Fuente JM, Baptista PV. *In vitro transcription and translation inhibition via DNA functionalized gold nanoparticles.* Nanotechnology. 2010;21(50):505101. doi: 10.1088/0957-4484/21/50/505101.
45. Giljohann DA, Seferos DS, Prigodich AE, Patel PC, Mirkin CA. *Gene regulation with polyvalent siRNA-nanoparticle conjugates.* J Am Chem Soc 2009;131:2072–2073.
46. Conde J, Rosa J, de la Fuente JM, Baptista PV. *Gold-nanobeacons for simultaneous gene specific silencing and intracellular tracking of the silencing events.* Biomaterials. 2013;34(10):2516–23. doi: 10.1016/j.biomaterials.2012.12.015. (http://www.sciencedirect.com/science/article/pii/S0142961212013956)
47. Rosa J, Conde J, de la Fuente JM, Lima JC, Baptista PV. *Gold-nanobeacons for real-time monitoring of RNA synthesis.* Biosens Bioelectron. 2012;36(1):161-7. doi: 10.1016/j.bios.2012.04.006 (http://www.sciencedirect.com/science/article/pii/S0956566312002229).
48. Conde J, Rosa J, Baptista P. *Gold-Nanobeacons as a theranostic system for the detection and inhibition of specific genes.* Community Contributed Protocol Exchange. 27 November 2013. doi:10.1038/protex.2013.088. (http://www.nature.com/protocolexchange/protocols/2881#/related-articles)
49. Mackey, Megan A.; Ali, Moustafa R. K.; Austin, Lauren A.; Near, Rachel D.; El-Sayed, Mostafa A. (2014-02-06). "The Most Effective Gold Nanorod Size for Plasmonic Photothermal Therapy: Theory and In Vitro Experiments". *The Journal of Physical Chemistry B*. **118** (5): 1319–1326. doi:10.1021/jp409298f. ISSN 1520-6106. PMC 3983380. PMID 24433049.
50. Niidome, Takuro; Yamagata, Masato; Okamoto, Yuri; Akiyama, Yasuyuki; Takahashi, Hironobu; Kawano, Takahito; Katayama, Yoshiki; Niidome, Yasuro (2006-09-12). "PEG-modified gold nanorods with a stealth character for in vivo applications". *Journal of Controlled Release*. **114** (3): 343–347. doi:10.1016/j.jconrel.2006.06.017.
51. Hainfeld, James et al. "The use of gold nanoparticles to enhance radiotherapy in mice." Phys. Med. Biol. 2004. Vol 49, N309–315
52. McMahon, Stephen et al. "Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles." Nature Scientific Reports http://www.nature.com/srep/2011/110620/srep00018/full/srep00018.html
53. Zhang, Zhiyang; Zhaopeng Chen; Shasha Wang; Chengli Qu; Lingxin Chen (2014). "On-site Visual Detection of Hydrogen Sulfide in Air Based on Enhancing the Stability of Gold NanoParticles". *ACS Applied Materials & Interfaces*. **6** (9): 6300–6307. doi:10.1021/am500564w.
54. Xu, S. et. al. *Gold nanoparticle-based biosensors.* Gold Bulletin. 2010, 43, p 29 –41.
55. J. Wang, R. Polsky and D. Xu, (title missing) Langmuir, 2001, 17, 5739.
56. J. Wang, D. Xu and R. Polsky, (title missing) J Am Chem Soc, 2002, 124, 4028.
57. M. C. Daniel and D. Astruc, (title missing) Chem Rev, 2004, 104, 293.
58. M. Hu, J. Chen, Z.Y. Li, L. Au, G.V. Hartland, X. Li, M. Marquez and Y. Xia, (title missing) Chem Soc Rev, 2006, 35, 1084.
59. S. Link and M.A. El-Sayed, (title missing) J. Phys. Chem. B, 1996, 103, 8410.
60. P. Mulvaney, (title missing) Langmuir, 1996, 12, 788.
61. H. Y. Lin, C. T. chen and Y. C. Chen, (title missing) Anal Chem, 200, 78, 6873
62. L. He, M.D. Musick, S. R. Nicewarner, F.G. Salinas, (title missing) Journal of the American Chemical Society, 2000, 122, 9071
63. A.M. Qi, I. Honma and H. Zhou, (title missing) Opt Lett, 2000, 25, 372
64. K.R. Brown, a.P Fox and M.J. Natan, (title missing) Journal of the American Chemical society, 1996, 118, 1154.
65. Y. Xiao, et. al. (title missing) Science, 2003,299, 1877.
66. A. Gole, et. al. (title missing) Langmuir, 2001, 17, 1674
67. A. Gole, et. al. *Colloids and Surfaces B: Biointerfaces,* 2002, 25, 129
68. M. Valden, X. Lai and D.W. Goodman, (title missing) Science, 1998, 281, 1647
69. Y. Lou, M.M. Maye, L. Han, J.Luo and C. –J. Zhong, (title missing) Chemical Communications, 2001, 473
70. M. Turner, V.B. Golovko, O.P Vaughan, P. Abdulkin, A. Berenguer-Murcia, M.S. Tikhov, B.F. Johnson and R.M Lambert, (title missing) Nature, 2008, 454, 981
71. Sperling, R. A.; Parak, W. J. (2010-03-28). "Surface modification, functionalization and bioconjugation of colloidal inorganic nanoparticles". *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*. **368** (1915): 1333–1383. doi:10.1098/rsta.2009.0273. ISSN 1364-503X. PMID 20156828.
72. Tauran, Yannick; Brioude, Arnaud; Coleman, Anthony W; Rhimi, Moez; Kim, Beonjoom (2013-08-26). "Molecular recognition by gold, silver and copper nanoparticles". *World Journal of Biological Chemistry*. **4** (3): 35–63. doi:10.4331/wjbc.v4.i3.35. ISSN 1949-8454. PMC 3746278. PMID 23977421.
73. Taguchi, Tomoya; Isozaki, Katsuhiro; Miki, Kazushi (2012-12-18). "Enhanced Catalytic Activity of Self-Assembled-Monolayer-Capped Gold Nanoparticles". *Advanced Materials*. **24** (48): 6462–6467. doi:10.1002/adma.201202979. ISSN 1521-4095.
74. Heinecke, Christine L.; Ni, Thomas W.; Malola, Sami; Mäkinen, Ville; Wong, O. Andrea; Häkkinen, Hannu; Ackerson, Christopher J. (2012-08-15). "Structural and Theoretical Basis for Ligand Exchange on Thiolate Monolayer Protected Gold Nanoclusters". *Journal of the American Chemical Society*. **134** (32): 13316–13322. doi:10.1021/ja3032339. ISSN 0002-7863. PMC 4624284. PMID 22816317.
75. Perumal, Suguna; Hofmann, Andreas; Scholz, Norman; Rühl, Eckart; Graf, Christina (2011-04-19). "Kinetics Study of the Binding of Multivalent Ligands on Size-Selected Gold Nanoparticles". *Langmuir*. **27** (8): 4456–4464. doi:10.1021/la105134m. ISSN 0743-7463.
76. McMahon, Jeffrey M.; Emory, Steven R. (2007-01-01). "Phase Transfer of Large Gold Nanoparticles to Organic Solvents with Increased Stability". *Langmuir*. **23** (3): 1414–1418. doi:10.1021/la0617560. ISSN 0743-7463.
77. Tyo, Eric C.; Vajda, Stefan. "Catalysis by clusters with precise numbers of atoms". *Nature Nanotechnology*. **10** (7): 577–588. doi:10.1038/nnano.2015.140.
78. Niu, Zhiqiang; Li, Yadong (2014-01-14). "Removal and Utilization of Capping Agents in Nanocatalysis". *Chemistry of Materials*. **26** (1): 72–83. doi:10.1021/cm4022479. ISSN 0897-4756.
79. Häkkinen, Hannu; Walter, Michael; Grönbeck, Henrik (2006-05-01). "Divide and Protect: Capping Gold Nanoclusters with Molecular Gold−Thiolate Rings". *The Journal of Physical Chemistry B*. **110** (20): 9927–9931. doi:10.1021/jp0619787. ISSN 1520-6106.
80. Reimers, Jeffrey R.; Ford, Michael J.; Halder, Arnab; Ulstrup, Jens; Hush, Noel S. (2016-03-15). "Gold surfaces and nanoparticles are protected by Au(0)–thiyl species and are destroyed when Au(I)–thiolates form". *Proceedings of the National Academy of Sciences*. **113** (11): E1424–E1433. doi:10.1073/pnas.1600472113. ISSN 0027-8424. PMC 4801306. PMID 26929334.

81. Park, Jong-Won; Shumaker-Parry, Jennifer S. (2014-02-05). "Structural Study of Citrate Layers on Gold Nanoparticles: Role of Intermolecular Interactions in Stabilizing Nanoparticles". *Journal of the American Chemical Society*. **136** (5): 1907–1921. doi:10.1021/ja4097384. ISSN 0002-7863.
82. Alkilany, A. M.; Murphy, C.J . (September 2010). "Toxicity and cellular uptake of gold nanoparticles: what we have learned so far?". *Nanoparticle Research*. **12** (7): 2313–2333. doi:10.1007/s11051-010-9911-8.
83. Rama, S.; Perala, K.; Kumar, S. (July 2013). "On the Mechanism of Metal Nanoparticle Synthesis in the Brust-Schiffrin Method". *Langmuir*. **29** (31): 9863–73. doi:10.1021/la401604q.
84. Murphy, C.J.; et., al. (March 2009). "Cellular uptake and cytotoxicity of gold nanorods: molecular origin of cytotoxicity and surface effects". *Small*. **5** (6): 701–708. doi:10.1002/smll.200801546.
85. Murphy, C.J.; et., al. (March 2009). "Cellular uptake and cytotoxicity of gold nanorods: molecular origin of cytotoxicity and surface effects". *Small*. **5** (6): 701–708. doi:10.1002/smll.200801546.
86. Takahashi, H.; et., al. (January 2006). "Modification of gold nanorods using phosphatidylcholine to reduce cytotoxicity.". *Langmuir*. **22** (1): 2–5. doi:10.1021/la0520029.
87. Rotello, V.M.; et., al. (June 2004). "Toxicity of Gold Nanoparticles Functionalized with Cationic and Anionic Side Chains.". *Bioconjugate Chemistry*. **15** (4): 897–900. doi:10.1021/bo049951i.
88. Murphy, C.J.; et., al. (January 2005). "Gold Nanoparticles Are Taken Up by Human Cells but Do Not Cause Acute Cytotoxicity.". *Small*. **1** (3): 325–327. doi:10.1002/smll.2004000093.
89. McNeil, S.E.; et., al. (June 2009). "Interaction of colloidal gold nanoparticles with human blood: effects on particle size and analysis of plasma protein binding profiles.". *Nanomedicine: Nanotechnology, Biology, and Medicine*. **5** (2): 106–117. doi:10.1016/j.nano.2008.08.001.
90. Chen, Y.S.; et., al. (May 2009). "Assessment of the In Vivo Toxicity of Gold Nanoparticles.". *Nanoscale Research Letters*. **4** (8): 858–864. doi:10.1007/s11671-009-9334-6.
91. Jeong, J.; et., al. (April 2009). "Acute toxicity and pharmacokinetics of 13 nm-sized PEG-coated gold nanoparticles.". *Toxicology and Applied Pharmacology*. **1** (1): 16–24. doi:10.1016/j.taap.2008.12.023.
92. Gref, R.; et., al. (November 2003). "Surface-engineered nanoparticles for multiple ligand coupling". *Biomaterials*. **24** (24): 4529–4537.
93. Astruc, D.; Boisselier, E. (April 2009). "Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity". *Chemical Society Reviews*. **38** (6): 1759–1782. doi:10.1039/b806051g.
94. Mohan, R.R.; et., al. (June 2013). "BMP7 Gene Transfer via Gold Nanoparticles into Stroma Inhibits Corneal Fibrosis In Vivo". *Plos One*. **8** (6): 1 –9. doi:10.1371/journal.pone.0066434.
95. Goodman, C.M.; McCusker, C.D.; Yilmaz, T.; Rotello, V.M. (June 2004). "Toxicity of Gold Nanoparticles Functionalized with Cationic and Anionic Side Chains". *Bioconjugate Chemistry*. **15** (4): 897–900. doi:10.1021/bo049951i.
96. Gratton, S. E. A.; Polhaus, P. D.; et. al (June 2007). "Nanofabricated particles for engineered drug therapies: A preliminary biodistribution study of PRINT™ nanoparticles". *J. Control Release*. **121** (1-2): 10–18. doi:10.1016/j.jconrel.2007.05.027.
97. Sonavane, G.; Tomoda, K.; Makino, K. (October 2008). "Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size.". *Colloids Surf. B*. **66** (2): 274–280. doi:10.1016/j.colsurfb.2008.07.004.
98. De Jong, W. H.; Hagens, W.I.; et. al. (April 2008). "Particle size-dependent organ distribution of gold nanoparticles after intravenous administration.". *Biomaterials*. **29** (12): 1912–1919. doi:10.1016/j.biomaterials.2007.12.037.
99. V. Amendola, M. Meneghetti, "Laser ablation synthesis in solution and size manipulation of noble metal nanoparticles", Phys. Chem. Chem. Phys., 2009,11, 3805–3821.
100. J. Turkevich, P. C. Stevenson, J. Hillier, "A study of the nucleation and growth processes in the synthesis of colloidal gold", Discuss. Faraday. Soc. 1951, 11, 55–75.
101. J. Kimling, M. Maier, B. Okenve, V. Kotaidis, H. Ballot, A. Plech, "Turkevich Method for Gold Nanoparticle Synthesis Revisited", J. Phys. Chem. B 2006, 110, 15700–15707.
102. G. Frens, "Particle size and sol stability in metal colloids", Colloid & Polymer Science 1972, 250, 736–741.
103. G. Frens, "Controlled nucleation for the regulation of the particle size in monodisperse gold suspensions", Nature (London), Phys. Sci. 1973, 241, 20 –22.
104. "Removal and Utilization of Capping Agents in Nanocatalysis." - Chemistry of Materials (ACS Publications). N.p., n.d. Web. 14 Nov. 2016. <http://pubs.acs.org/doi/abs/10.1021/cm4022479>.
105. Pong, B.-K.; Elim, H. I.; Chong, J.-X.; Trout, B. L.; Lee, J.-Y., New Insights on the Nanoparticle Growth Mechanism in the Citrate Reduction of Gold(III) Salt: Formation of the Au Nanowire Intermediate and Its Nonlinear Optical Properties. *J. Phys. Chem. C* 2007, 111 (17), 6281-6287. doi: 10.1021/jp068666o
106. M. Brust; M. Walker; D. Bethell; D. J. Schiffrin; R. Whyman (1994). "Synthesis of Thiol-derivatised Gold Nanoparticles in a Two-phase Liquid-Liquid System". *Chem. Commun.* (7): 801–802. doi:10.1039/C39940000801.
107. Manna, A.; Chen, P.; Akiyama, H.; Wei, T.; Tamada, K.; Knoll, W. (2003). "Optimized Photoisomerization on Gold Nanoparticles Capped by Unsymmetrical Azobenzene Disulfides". *Chem. Mater.* **15** (1): 20–28. doi:10.1021/cm0207696.
108. Gao, Jie; Huang, Xiangyi; Liu, Heng; Zan, Feng; Ren, Jicun (2012-03-06). "Colloidal Stability of Gold Nanoparticles Modified with Thiol Compounds: Bioconjugation and Application in Cancer Cell Imaging". *Langmuir*. **28** (9): 4464–4471. doi:10.1021/la204289k. ISSN 0743-7463.
109. Bekalé, Laurent, Saïd Barazzouk, and Surat Hotchandani. "Beneficial Role of Gold Nanoparticles as Photoprotector of Magnesium Tetraphenylporphyrin." SpringerReference (n.d.): n. pag. Web. 14 Nov. 2016.
110. "Phosphine-Stabilized Gold Nanoparticles." Nanomanufacturing Process Database (n.d.): n. pag. Web. 14 Nov. 2016. <http://www.chemistry.illinois.edu/research/inorganic/seminar_abstracts/2008-2009/Shen.Abstract.pdf>.
111. "Phosphine-Stabilized Gold Nanoparticles." Nanomanufacturing Process Database (n.d.): n. pag. Web. 14 Nov. 2016. <http://www.chemistry.illinois.edu/research/inorganic/seminar_abstracts/2008-2009/Shen.Abstract.pdf>.
112. S.D. Perrault; W.C.W. Chan (2009). "Synthesis and Surface Modification of Highly Monodispersed, Spherical Gold Nanoparticles of 50-200 nm". *J. Am. Chem. Soc*. **131** (47): 17042–3. doi:10.1021/ja907069u. PMID 19891442.
113. M.N. Martin; J.I. Basham; P. Chando; S.-K. Eah (2010). "Charged Gold Nanoparticles in Non-Polar Solvents: 10-min Synthesis and 2D Self-Assembly". *Langmuir*. **26** (10): 7410–7417. doi:10.1021/la100591h. A 3-min demonstration video for the Martin synthesis method is available at YouTube (https://www.youtube.com/watch?v=nqkwM9o1s-w)
114. Kalishwaralal, Kalimuthu; Deepak, Venkataraman; Ram Kumar Pandian, Sureshbabu; Gurunathan, Sangiliyandi (1 November 2009). "Biological synthesis of gold nanocubes from Bacillus licheniformis". *Bioresource Technology*. **100** (21): 5356–5358. doi:10.1016/j.biortech.2009.05.051.
115. Julien R.G. Navarro, Frédéric Lerouge, Cristina Cepraga , Guillaume Micouin, Arnaud Favier, Denis Chateau, Marie-Thérèse Charreyre , Pierre-Henri Lanoë, Cyrille Monnereau, Frédéric Chaputa,Sophie Marotte, Yann Leverrier, Jacqueline Marvel, Kenji Kamada, Chantal Andraud, Patrice L. Baldeck, Stephane Parola Nanocarriers with ultrahigh chromophore loading for fluorescence bio-imaging and photodynamic therapy, Biomaterials, 2013, 34, 8344–8351
116. Baigent, CL & Müller, G. (1980) A colloidal gold prepared using ultrasonics (http://link.springer.com/article/10.1007%2FBF01975154?LI=true), *Experientia* 15. 4. Volume 36, Issue 4, pp 472–473.
117. Jianling Zhang; Jimin Du; Buxing Han; Zhimin Liu; Tao Jiang; Zhaofu Zhang (2006). "Sonochemical Formation of Single-Crystalline Gold Nanobelts". *Angew. Chem*. **118** (7): 1134–7. doi:10.1002/ange.200503762.
118. Sakai et al., 2005, *Mechanism of Gold Metal Ion Reduction, Nanoparticle Growth and Size Control in Aqueous Amphiphilic Block Copolymer Solutions at Ambient Conditions,* J. Phys. Chem. B, 2005, 109 (16), pp 7766–7777 (abstract) (http://pubs.acs.org/doi/full/10.1021/jp046221z)
119. Ray et al., 2011, *Synthesis and Characterization of High Concentration Block Copolymer-Mediated Gold Nanoparticles,* Langmuir, 2011, 27 (7), pp 4048 –4056 (abstract) (http://pubs.acs.org/doi/abs/10.1021/la2001706)
120. Nune, S.K.; Nripen, C.; Shukla, R.; Katti, K.; Kulkarni, R.R.; Thilakavathy, S.; Mekapothula, S.; Kannan, R.; Katti, K.V. (2009). "Green nanotechnology from tea: phytochemicals in tea as building blocks for production of biocompatible gold nanoparticles" *J. Chem Mater.* (19) 2912-2920. doi:10.1039/b822015h
121. Haiss, Wolfgang, et al. "Determination of Size and Concentration of Gold Nanoparticles from UV-Vis Spectra." Analytical Chemistry 79.11 (2007): 4215 –21. Print.
122. Nune, Satish K., et al. "Green Nanotechnology from Tea: Phytochemicals in Tea as Building Blocks for Production of Biocompatible Gold Nanoparticles." Journal of materials chemistry 19.19 (2009): 2912–20. Print.
123. Pattanayak, Monalisa, and PL Nayak. "Green Synthesis of Gold Nanoparticles using Elettaria Cardamomum (ELAICHI) Aqueous Extract." World 2.1 (2013): 01-5. Print.
124. Chanda, Nripen, et al. "An Effective Strategy for the Synthesis of Biocompatible Gold Nanoparticles using Cinnamon Phytochemicals for Phantom CT Imaging and Photoacoustic Detection of Cancerous Cells." Pharmaceutical research 28.2 (2011): 279-91. Print.
125. Subhankari, Ipsa, and PL Nayak. "Synthesis of Copper Nanoparticles using Syzygium Aromaticum (Cloves) Aqueous Extract by using Green Chemistry." World 2.1 (2013): 14-7. Print.
126. KahkashanMazhar, AmbreenGull Muazzam, and Mohammad Ismail. "Novel and Cost-Effective Green Synthesis of Silver Nano Particles and their in-Vivo Antitumor Properties Against Human Cancer Cell Lines." Print.
127. Lee, M.-J.; Lim, S.-H.; Ha, J.-M.; Choi, S.-M. "Green Synthesis of High-Purity Mesoporous Gold Sponges Using Self-Assembly of Gold Nanoparticles Induced by Thiolated Poly(ethylene glycol)" *Langmuir* 2016, 32, 5937-5945. doi: 10.1021/acs.langmuir.6b01197
128. Qi, Z.; Vainio, U.; Kornowski, A.; Ritter, M.; Weller, H.; Jin, H.; J., W., "Porous Gold with a Nested-Network Architecture and Ultrafine Structure." *Adv. Funct. Mater.* 2015, 25, 2530-2536. doi:10.1002/adfm.201404544

129. Bayazit, M. K.; Yue, J.; Cao, E.; Gavriilidis, A.; Tang, J., *Controllable Synthesis of Gold Nanoparticles in Aqueous Solution by Microwave Assisted Flow Chemistry.* ACS Sustainable Chem. Eng. 2016, Article ASAP. doi:10.1021/acssuschemeng.6b01149

Further reading

- Boisselier, E.; Astruc, D (2009). "Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity". *Chemical Society Reviews*. **38** (6). pp. 1759–1782. doi:10.1039/b806051g. - " This critical review provides an overall survey of the basic concepts and up-to-date literature results concerning the very promising use of gold nanoparticles (AuNPs) for medicinal applications."
- Conde, J.; Doria, G; Baptista, P (2012). "Noble Metal Nanoparticles Applications in Cancer". *Journal of Drug Delivery*. **2012** (6). pp. 1–12. doi:10.1155/2012/751075. - "This review provides insights of the available noble metal nanoparticles for cancer therapy, with particular focus on those already being translated into clinical settings."
- Conde, J.; Rosa, J; Lima, J.C.; Baptista, P.V. (2012). "Nanophotonics for Molecular Diagnostics and Therapy Applications". *International Journal Photoenergy*. **2012**.

External links

- Moriarty, Philip. "Au – Gold Nanoparticle". *Sixty Symbols*. Brady Haran for the University of Nottingham.
- Point-by-point methods for citrate synthesis and hydroquinone synthesis of gold nanoparticles are available here (http://www.stevenperrault.com/lab-methods/).

Wikimedia Commons has media related to ***Colloidal gold***.

Retrieved from "https://en.wikipedia.org/w/index.php?title=Colloidal_gold&oldid=754946912"

Categories: Gold | Nanoparticles | Colloids