

Therapeutic possibilities of plasmonically heated gold nanoparticles

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Nanoparticles of gold, which are in the size range 10–100 nm, undergo a plasmon resonance with light. This is a process whereby the electrons of the gold resonate in response to incoming radiation causing them to both absorb and scatter light. This effect can be harnessed to either destroy tissue by local heating or release payload molecules of therapeutic importance. Gold nanoparticles can also be conjugated to biologically active moieties, providing possibilities for targeting to particular tissues. Here, we review the progress made in the exploitation of the plasmon resonance of gold nanoparticles in photo-thermal therapeutic medicine.

Introduction

Metallic gold, either in the form of bulk surfaces or as nanoparticles, is widely used in the emerging and highly interdisciplinary field of nanotechnology [1–3]. Many biodiagnostic applications of gold nanoparticles, or electrodes, have been developed since the 1970s [4–10]; however, the rational application of gold nanoparticles in therapeutic situations is a largely undeveloped field. Two properties of gold nanoparticles make them particularly suitable for therapeutic applications: antibodies and other biological molecules can be readily attached to the surface of gold nanoparticles, and the plasmon resonances of gold nanoparticles of certain shapes cause them to have photon capture cross-sections that are four to five orders of magnitude greater than those of photothermal dyes [11]. These attributes are exploited to obtain the localized heating, or drug release, underlying the therapeutic applications.

Excellent reviews of the basic physical, chemical and optical properties of gold nanoparticles, and their other applications, are available [1,12], and the medical uses of soluble gold compounds have been discussed by Shaw [13]. The general medical applications of nanoparticles have been reviewed by Salata [14], while Moghimi *et al.* [15] have reviewed the use of nanoparticles in drug-delivery schemes not involving light. Finally, the use of light to control drug delivery in liposomal systems was summarized by Shum [16]. However, while the medical

applications of one kind of gold particle, the ‘nanoshell’, have been widely discussed [17–19], no broad synopsis of the recent developments in the photo-thermal, therapeutic applications of gold nanoparticles exists in the literature at this time and we address this topic here.

Relevant properties of gold nanoparticles

The chemical and physical properties of gold have been reviewed recently by Pyykko [20]. From a therapeutic point of view, there are two properties of gold that are most relevant: resistance to oxidation and plasmon resonance with light. The plasmon resonance for ordinary gold nanospheres is at ~520 nm, in the middle of the visible spectrum, but this can be red-shifted into the near infrared (NIR), with excitation wavelengths of 800–1200 nm required for more complex shapes, such as nanorods (Box 1). This is useful because body tissue is moderately transparent to NIR light [11,17,21], thereby providing an opportunity for therapeutic effects in deep tissues.

Gold or silver metallo-dielectric core-shell particles offer another route for the spectral control of both absorption and scattering of light, particularly if the core is a dielectric (most commonly gold sulfide, silica or polystyrene) and the shell is a metal. The spectral properties of such shapes can be controlled by varying the relative dimensions of the core and the shell (Figure 1) [19,22–27]. Several groups have reported methods for the synthesis of these shapes, notably Halas *et al.* at Rice University, Texas USA. This group have published several papers [9,11,17–19,21,27–33] and patents [34–38] on the manufacture and potential medical applications of these particles. Although the term nanoshell is used in North America to refer to these particles, the term core-shell particle is more common in Europe [39,40] for both metal-on-dielectric and dielectric-on-metal particles.

Biomedical exploitation of gold nanoparticles

Targeting strategies for nanoparticles

A disadvantage of many drug-based therapies (particularly when administered orally or intravenously) is that the compound does not localize to the target site but is widely dispersed. Treatments based on nanoparticles can aid accumulation of the therapeutic agent either by passive targeting, where the body concentrates inert

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Box 1. Optical properties of metal nanoparticles

A nanoscale electronic effect, known as the plasmon resonance effect, causes metallic nanoparticles to absorb and scatter electromagnetic radiation of wavelengths considerably larger than the particles themselves. These effects are particularly noticeable in the visible part of the spectrum for gold, silver and copper particles: in the case of gold nanospheres, the plasmon resonance and, hence, absorption is ~520 nm (corresponding to green light). A proportion of the incident light is scattered, but the absorbed light will cause heating in the particles resulting in a highly localized increase in temperature, which is exploited in the various proposed photo-thermal therapeutic uses of gold nanoparticles. Further background information on the optical phenomena

involved may be found in a standard text, such as that of Bohren and Huffman [54].

It may be convenient to shift the wavelength of maximum absorption into the near infrared because the body is more transparent at those wavelengths [11,21]. This can be achieved with gold nanoshells [17] by enhancing the dipole-dipole interaction between aggregated gold nanospheres [44,55,56] or by decreasing the symmetry of the particles, for example, through the formation of nanorods [57]. Gold nanorods have two plasmon absorption peaks, and the position of the second peak can be moved deep into the near infra-red (NIR) region by controlling the aspect ratio of the nanorod. Gold 'nano-caps' [58] have similar red-shifted extinction spectra.

nanoparticles, or by active targeting, where functional modification of the surface of the gold particle enhances the therapeutic delivery system resulting in specific tissue targeting [15]. The two approaches are illustrated in Figure 2 and further compared in the text below.

Passive targeting

Nanoparticle colloids can be designed so that the particles are big enough to be retained in the liver and spleen but pass relatively freely through the other organs [15]. This type of passive targeting has been used in the radiotherapeutic treatment of liver cancers, where the sinus endothelium of that organ has openings of 150 nm in diameter, whereas the spleen filters out particles greater than 250 nm in size [15]. Similarly, the fact that tumour vasculature is somewhat more permeable than that of healthy tissue [41] has also been exploited to concentrate nanoparticles. O'Neal *et al.* reported that nanoshells with diameters of 130 nm passed preferentially through the walls of vessels and were deposited in the surrounding tumorous tissue, where they are concentrated [21]. This phenomenon, termed extravasation, provides another passive method to concentrate particles of up to 300 nm diameter in some tumours or inflamed tissues [15].

Active targeting

Reliance on size-specific filtration for the retention of nanoparticles has obvious limitations. A more sophisticated approach is to modify the surface of the nanoparticle by the addition of an antibody or ligand with affinity for the desired target; however, this approach also has limitations owing to non-specific binding and the potential activation of the normal host immune response. The probability of an interaction between nanoparticles and the immune system can be substantially reduced by using so-called stealth technologies. These involve coating the nanoparticle with a self-assembled layer of a thiolated PEG (poly-ethyleneglycol) [2,15,42] or liposome, rendering the surfaces of these particles inert with respect to protein absorption. Paradoxically, if a particle is so well coated that it becomes invisible to the immune system, it will also probably lose its ability to bind to specific receptors.

Once the gold nanoparticle is concentrated at the desired site, it is activated through the absorption of radiation of an appropriate wavelength. Depending on the design of the particle, this action could deliver one of two

therapeutic payloads: the localized generation of heat or the localized release of a chemical. Additionally, the attached gold particles can be used to simultaneously track or image the cells [9,11].

Hyperthermal therapy

Local application of heat is a well-known concept in therapeutic medicine that has been explored extensively for the treatment of cancer and other conditions. Energizing sources, such as infrared lamps, ultrasound or lasers, can be used in the process, but there is always the problem of limiting the heat generated to the region of the target tissue [43]. As mentioned earlier, the problem can be solved, in part, by using gold nanoparticles designed to absorb in the NIR spectrum such that the resulting localized heating causes irreversible thermal cellular destruction [18,19]. Although dyes have been used

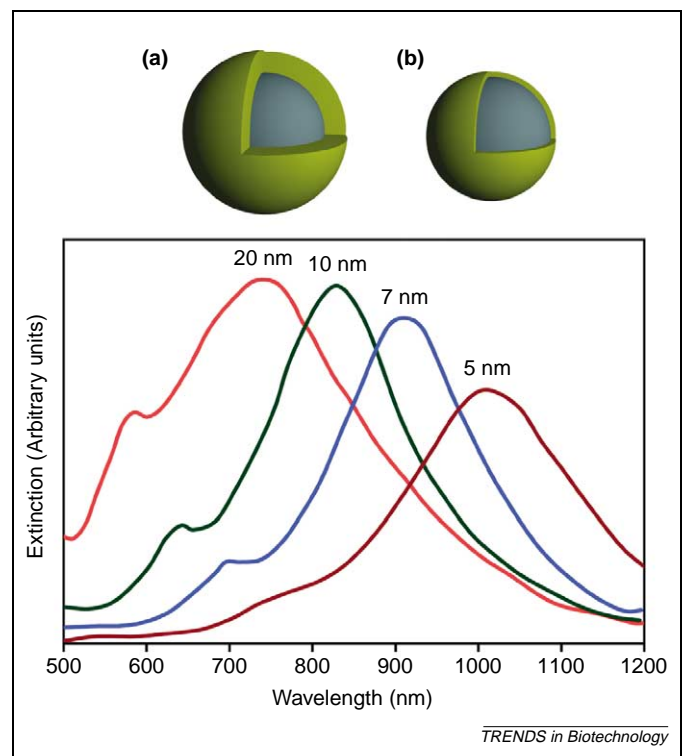


Figure 1. The optical response of gold nano-shells of different sizes illustrating how the extinction peak is red-shifted for relatively thinner shells. (a) 60 nm core radius with 20 nm shell, (b) 60 nm core radius with 6 nm shell. Graph shows extinction spectra corresponding to various thicknesses of gold shells. Adapted and redrawn with permission from Loo *et al.* [11].

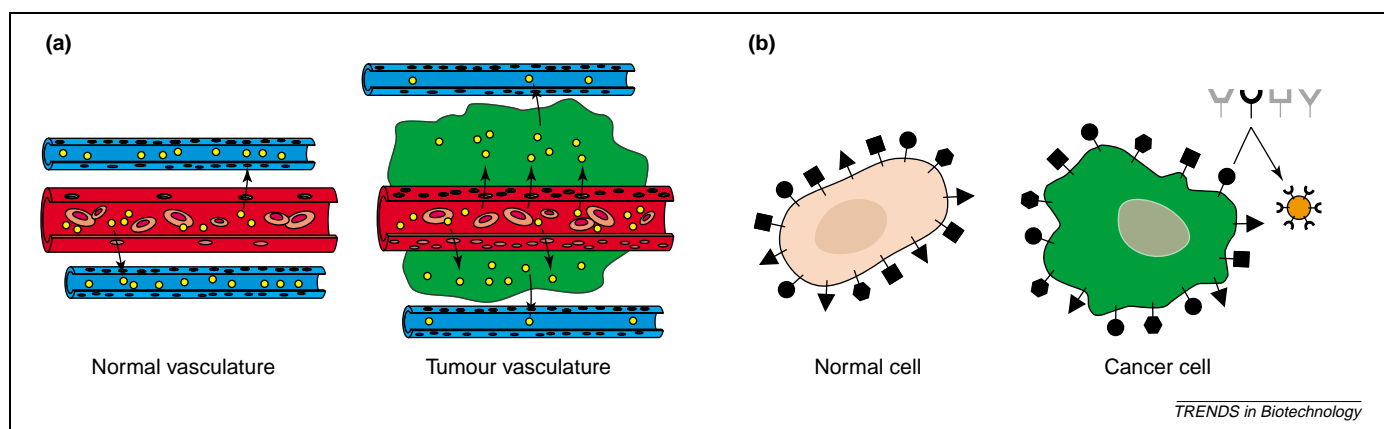


Figure 2. Passive and active targeting of nanoparticles. (a) Passive targeting using the enhanced permeability and retention (EPR) effect, which exploits the increased permeability of the tumour vasculature (extravasation) to concentrate therapeutic agents. (b) Active targeting of a carcinoma by an antibody-functionalized nanoparticle. Once concentrated at the target site, the therapeutic payload is released in response to light of a specific wavelength. Redrawn with permission from McNeil [58].

for this purpose, particles such as gold nanoshells have absorption efficiencies that are many orders of magnitude greater than dyes and are not affected by photobleaching [18,21]. Furthermore, as we have seen, there are ways to target nanoparticles that are not available for pharmaceutical compounds solubilized *in vivo*.

The first account of the use of gold particles in hyperthermal therapy was published in 2003 [18,36]. In this, and follow-up work by Halas and co-workers, gold-on-silica nanoshells were used to target breast carcinoma cells, actively, using the HER2 antibody [11]. This initial report was soon complemented by an account where the extravasation phenomenon was exploited to concentrate PEG-sheathed gold-on-silica nanoshells by passive targeting in an *in vivo* murine model [21]. In the Halas study, NIR irradiation led to a rise in the temperature of the target regions of between 40 to 50°C, which selectively destroyed the carcinomas. The survival rate of mice treated in this manner was excellent compared with the controls.

Interestingly, the optical absorption spectrum of the gold particles used in the initial work [18] had a very broad peak and did not correspond to one representative of a particularly well defined dispersion of nanoshells. Spectra of this type are also obtained with aggregated dispersions of solid gold nanospheres [44]. The therapeutic effect can also be obtained with particle morphologies other than nanoshells. This has been elegantly shown by Pitsillides *et al.* [45], who selectively destroyed CD8+ lymphocytes in a mixed CD8+ and CD8- lymphocyte culture using ordinary colloidal gold nanoparticles. The particles were conjugated to a CD8+ -specific antibody and used together with a 532 nm laser, resulting in highly selective apoptosis of the CD8+ population. Furthermore, systematic variations in this experimental technique revealed conditions that selectively permeabilized the cell membranes of the target population for up to two minutes, coupled with only a modest lethality. This provides a unique, and hitherto scarcely exploited, therapeutic mode to access intracellular targets.

Although not an effect of plasmon resonance, there is an additional effect that causes enhanced absorption of X-ray radiation at the interface between materials of high and low atomic number leading to a localized generation of

heat. For example, the injection of 1.9 nm gold nanoparticles into murine tumours, followed by x-ray irradiation, led to destruction of the tumours [46]. In common with others [47], these workers found that the excess gold nanoparticles were cleared by the kidneys, and that they were not toxic to the mice.

Drug delivery

Here, the options available include encapsulating the payload inside a gold core-shell particle, impregnating a larger drug-containing nano- or microparticle with suitably designed gold particles or binding the payload to the outer surface of a gold nanoparticle. In all these cases, once the particle is at the target tissue, release of the payload is induced by plasmonic heating. To afford the degree of precision required for tumour targeting, and to achieve the correct excitation wavelength, it is envisaged that the source of light would need to be a laser. Gold nanoparticles are sufficiently small that, in principle, they might be capable of delivering a payload of therapeutic agent, or heat, directly into the cytoplasm or nucleus of the target cell [15,48,49].

The first description of photo-activated drug-release by plasmonically active particles was in 2000 [17,27], followed by a related US patent a little later [35]. In both cases, the work exploited a polymer-gel impregnated with gold nanoshells to give gold-on-gold-sulphide core-shell particles. Although this type of nanoshell was discovered in 1994 by Zhou [26], the novel aspect of this work was its incorporation into a polymer composite with the intention of securing controlled drug-release.

Recently, the plasmonic photo-activation of hollow polymer-capsules containing model drugs has been demonstrated. Skirtach and colleagues described a scheme whereby silver nanoparticles were incorporated into hollow polyelectrolyte capsules. These were ruptured by the heat generated from illumination with a laser, causing the capsules to release their contents [50]. Silver nanoparticles have a higher frequency plasmon resonance than gold particles, but the principles are otherwise the same. Soon after, Caruso and colleagues used gold nanoparticles in a similar role [51,52]. In this case, the illuminate-and-burst principle was successfully used to

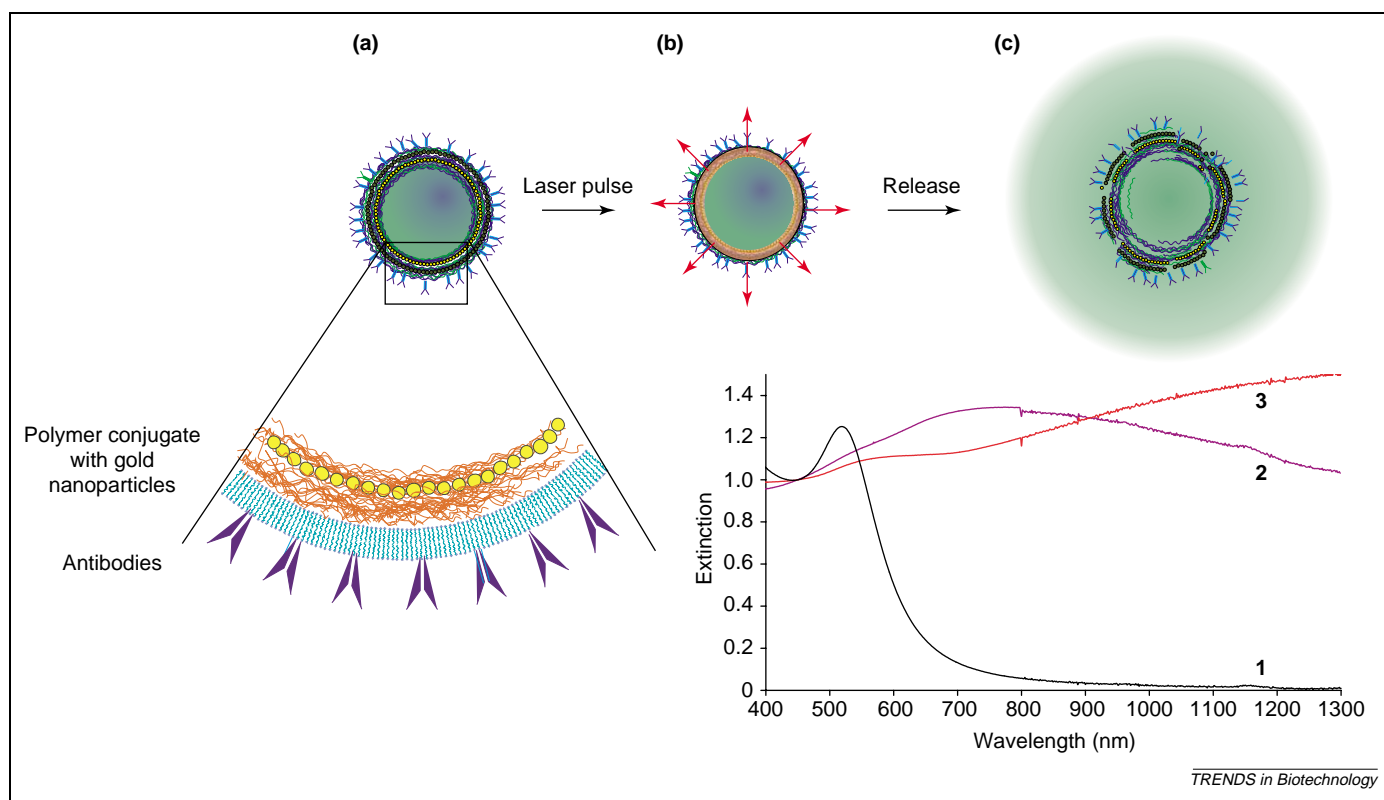


Figure 3. Controlled delivery of a chemical payload. The antibody-functionalized polymer capsule (a) binds to the target (*Micrococcus lysodeikticus*), and application of laser light causes the gold nanoparticles in the shell of the capsule to heat up (b), bursting the container and releasing the therapeutic agent in a localized area (c). Representative optical extinction spectra are shown for isolated gold nanoparticles (1), a poly-electrolyte shell containing a single layer of aggregated gold particles (2), and a shell containing three layers of gold particles (3). Reproduced with permission from Radt *et al.* [51].

release lysozyme to destroy the bacterium *Micrococcus lysodeikticus* – a schematic illustration of this is shown in Figure 3. In a further modification, the capsules were coated with a lipid bi-layer that was in turn decorated with antibodies [51].

A related idea is to bind the drug to the outside of a gold nanoparticle using, for example, a light-sensitive and conformation-changing molecule, such as spyropyran [53], to hold it in place. When spyropyran is irradiated by light in the ultraviolet part of the spectrum (320 nm), it undergoes a conformation change from an open form to a closed form, where the former can form complexes with amino acids; these complexes are destroyed when the molecule reverts to the closed form, and the amino acids are released [53]. Gold is an ideal substrate particle because it provides a convenient chemistry for attachment. However, the optical properties of gold are not exploited in this example. Targeting of such particles is also achieved by passive means only, but, once again, the localization of the therapeutic effect can only be achieved with a light source.

Box 2. Outstanding questions

Although most evidence suggests that colloidal gold particles are chemically inert *in vivo*, the issue is not definitively settled and requires further study. Certainly, it is known that such particles will be ingested by cells of the immune system unless rendered invisible by one of the so-called stealth technologies, and the overall implications of this need to be considered. Of course, removal of particles from the vasculature by leukocytes is particularly problematic with respect to

It has also been demonstrated that tumour necrosis factor (TNF) can be attached to gold nanoparticles, and these concentrated readily in murine tumours with beneficial results [47]. In this example, targeting is by extravasation and essentially passive in nature. Although no photo-activation of the payload was invoked in this particular work, it is probable that plasmonic heating of the gold particles, if it had been attempted, would have influenced the outcome.

One limitation of these drug delivery schemes is that the volume of payload that can be carried by individual nanoparticles is very limited. In the absence of any external scheme to trigger release, the concentration of therapeutic agent released by gradual diffusion, or owing to the breakdown of the packaging, might be too low to be effective [15].

Future developments

Despite many advances in this field, there is still a significant requirement for new technologies that will allow the earlier treatment of diseases such as cancer,

actively-targeted nanoparticles, which, by definition, need to expose some antigenic structure on their exterior surface. Perhaps there will be a short period of opportunity available to such particles to be delivered to their target sites before the immune system can mount a full reaction. Finally, one of the most interesting challenges is whether it will be feasible to target intracellular pathogens, actively, using functionalized nanoparticles, given that the antigenic properties of such pathogens are usually well concealed.

particularly if they also offer greater specificity and are cost effective. It is expected that development of the techniques described above will continue to take place, particularly in respect of active targeting. In addition, it is probable that the chemical- and physical-based therapies reviewed above will be complemented by gene therapies delivered by nanoparticles.

It is apparent that gold nanoparticles have unique chemical and physical properties that facilitate and commend their use in these applications, despite some questions that remain unanswered (Box 2). In particular, their optical properties and flexible surface chemistry permit their use in photo-thermal therapeutic treatments. The efficiency of the process can be enhanced considerably by exploiting various passive targeting strategies to concentrate the nanoparticles in the tissue to be treated. In principle, active targeting of the nanoparticle is also possible, although further work on methods to evade the immune system en route to the target also need to be considered.

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