Global Journal of Science Frontier Research: a
Physics and Space Science
Volume 20 Issue 11 Version 1.0 Year 2020
Type : Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4626 & Print ISSN: 0975-5896

Gold Nanoparticles as Source of Heat for Medical Treatment: A Review

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GJSFR-A Classification: *FOR Code: 240599*

GOLDNANOPARTICLESASSOURCEOFHEATFORMEDICALTREATMENTAREVIEW

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Gold Nanoparticles as Source of Heat for Medical Treatment: A Review

Ayushi Tyagi [α] & SS Verma [σ]

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I. Introduction

New properties emerge when the size of a matter is reduced from bulk to the nanometer scale [1,2]. These new properties, including optical, magnetic, electronic, and structural properties, make nano-sized particles (generally 1–100 nm) very promising for a wide range of biomedical applications such as cellular imaging, molecular diagnosis and target therapy depending on the structure, composite and shape of the nanomaterials [3]. The enchantment of Au NPs is reflected in their intense colour, originates from the basic photophysical response that does not exist to non-metallic particles. Noble metals and gold in particular lend themselves well to the synthesis nanoscale materials, thanks to their resistance to aging (oxidation), even in a divided form. Gold nanoparticles, can be obtained in colloidal form by chemical synthesis.

a) *Predominance of gold over other noble metals*

The predominance of gold over other noble metals is justified by its unique combination of advantages: (i) They exhibit varying colors, ranging from red to violet as their size decreases. Other colors like green and blue can be obtained by also playing on their shape. Gold leads to resonances that can be tuned from the visible to the (near infrared region) NIR, by adjusting the size and the shape of the NPs(since this alters their photothermal and photoacoustic properties, allowing for the utilization of different wavelengths of light, such as light in the near-infrared spectrum)(near-infrared (NIR) light has much greater body transparency making it preferable for PTT.); (ii) gold offers rich and simple surface chemistry that allows functionalization of gold NPs with a variety of chemical compounds; (iii) It has been recognized for its bacteriostatic, anticorrosive, and antioxidative properties i.e., resistance to corrosion and oxidation. their resistance to aging (oxidation), oxidation of gold remains very weak and (iv) gold is not cytotoxic (safely excreted through the urinary system) [4–5]. Colloidal gold exhibits localized plasmon surface resonance (LPSR), meaning that gold nanoparticles can absorb light at specific wavelengths, resulting in photoacoustic and photothermal properties, making them potentially useful for hyperthermic cancer treatments and medical imaging applications. They exhibit varying colors, ranging from red to violet as their size decreases. Other colors like green and blue can be obtained by also playing on their shape. Absorbed light is converted to heat via the nonradiative properties.

b) *Nano sources of heat*

For a long time, the absorption and the subsequent NP temperature increase have been considered as side effects in plasmonics applications, which focused on the optical properties of metal NPs. Only recently have scientists realized that this enhanced light absorption, turning metal NPs into ideal nano-sources of heat remotely controllable using light, provides an unprecedented way to control thermal-induced phenomena at the nanoscale [10]. The heat generation is directly proportional to the square of the electric field inside the metal. This is an important aspect to consider when designing efficient plasmonic nano-sources of heat. This heat generation in metal nanoparticles is described, under both continuous and pulsed illumination. The corresponding energy can escape in the environment via three processes: (i) diffusion, (ii) convection and (iii) radiation, although the main kind of energy transfer in plasmonics remains diffusion.

c) *Localized surface plasmons (LSPs)*

Localized surface plasmons (LSPs), are responsible for both enhanced light scattering and enhanced light absorption. The interaction of the electromagnetic field with nanostructure at resonance

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conditions is characterized by a significant enhancement of the scattering and absorption cross sections that may be orders of magnitude higher compared to these at out of resonance conditions [7,8]. On this basis technology of nanoparticle photothermal cancer cell therapy and biological object imaging is developed [9].

d) Surface Plasmons and Surface Plasmon Resonance Sensing (SPR)

Unique phenomenon to plasmonic (noble metal) nanoparticles leads to strong electromagnetic fields on the particle surface and consequently enhances all the radiative properties such as absorption and scattering [11]. These optical properties are a consequence of the dielectric confinement in these objects whose size is less than the wavelength of the excitatory light and which is at the origin of the well-known phenomenon of surface plasmon resonance (SPR), which dominates the extinction spectrum in the visible domain [6].SPR of metallic nanoparticles has significant applications in optics, communications and biosensors. These are the changes caused by increasing influence of certain electromagnetic surface modes—coherent fluctuations of electron charges on metal boundary called surface plasma oscillations or plasmons. Excitation of surface plasmons takes place, when the surface of the metal is exposed to incoming electrons or photons. Plasmons are strongly bound to the incident surface with their maximum intensity at the surface and disappear quickly with increasing distance from the surface. Therefore, they are very sensitive to the surface properties.

e) Plasmonic resonance

Plasmonic resonance occurs when conduction band electrons on metal nanoparticle surface collectively oscillates with same frequency as that irradiated light. This plasmonic resonance has attracted great attention because of large electromagnetic field enhancements near metal nanoparticle and the regulating resonance wavelength with change in material, size, shape and surrounding medium of metallic nanoparticle. Incorporation of liquid metal nanoparticles in plasmonic provides unique properties towards sensing (heart rate monitors etc.)

i. *Surface plasmon resonance*

When a metal particle is exposed to light, the oscillating electromagnetic field of the light induces a collective coherent oscillation of the free electrons (conduction band electrons) of the metal. This electron oscillation around the particle surface causes a charge separation with respect to the ionic lattice, forming a dipole oscillation along the direction of the electric field of the light. The amplitude of the oscillation reaches maximum at a specific frequency, called surface plasmon resonance (SPR) [12–13]. The SPR induces a strong absorption of the incident light and thus can be measured using a UV–Vis absorption spectrometer. The SPR band is much stronger for plasmon nanoparticles (noble metal, especially Au and Ag) than other metals. The SPR band intensity and wavelength depends on the factors affecting the electron charge density on the particle surface such as the metal type, particle size, shape, structure, composition and the dielectric constant of the surrounding medium, as theoretically described by Mie theory [14] Surface-plasmon resonance-enhanced optical properties of colloidal gold nanoparticles directed towards recent biomedical applications with an emphasis on cancer diagnostics and therapeutics.

ii. *Surface plasmon absorption and scattering*

The energy loss of electromagnetic wave (total light extinction) after passing through a matter results from two contributions: absorption and scattering processes. Light absorption results when the photon energy is dissipated due to inelastic processes. Light scattering occurs when the photon energy causes electron oscillations in the matter which emit photons in the form of scattered light either at the same frequency as the incident light (Rayleigh scattering) or at a shifted frequency (Raman scattering). The frequency shift corresponds to the energy difference created molecular motion within the matter (molecular bond rotations, stretching or vibrations). Due to the SPR oscillation, the light absorption and scattering are strongly enhanced, 5–6 orders of magnitude stronger than most strongly absorbing organic dye molecules and then the emission of most strongly fluorescent molecules, respectively [15]

II. Objectives

a) To study the Applications of gold nanoparticles as nano sources of heat

- Nanoparticles applications as nano sources of heat,
  - photothermal cancer therapy
  - drug and gene delivery
  - photoacoustic imaging
  - plasmonic-induced nanochemistry
  - photothermal imaging
  - Nano-surgery
- For each application, particular attention will be paid to

(i) the pioneering works,
(ii) the subsequent pivotal works that introduced the variants and new concepts and (iii) the current state of the art and remaining challenges.

- Brief idea about other applications like protein denaturation, heat-assisted magnetic recording, thermo-plasmonics for Cell Biology.

III. Applications

a) Plasmonic Photothermal Therapy (PPTT)

i. *Hyperthermia for Cancer Therapy (initial approach)*

- Killing cells by heating them above a certain temperature threshold has long been considered a means to cure cancer, since as early as the late 1800s [16, 17, 18], sometimes applied as an adjunctive therapy with various established cancer treatments such as radiotherapy and chemotherapy [19].
- A temperature rises at around 41–48◦C is in principle sufficient to induce cell death. This process is called *hyperthermia*.
- The application of even higher temperatures (48–60◦C) is termed *ablation*. In any case, an efficient photothermal treatment relies on a subtle interplay between temperature and exposure time [20].

ii. *Hyperthermia using Plasmonic Nanoparticles*

Photothermal therapy uses photothermal nano-agents to treat disease by local hyperthermia [21]. The idea of using gold nanoparticles as nanosources of heat for photothermal cancer therapy is one of the most ancient and the most promoted application of thermoplasmonics (Plasmonic Photothermal Therapy (PPTT)). PTT using spherical gold nanoparticles [22] can be achieved with pulsed or cw visible lasers due to the SPR absorption in the visible region and thus such treatment is suitable for shallow cancer (e.g. skin cancer). The cell death is attributed mainly to the cavitation damage induced by the generated micro-scale bubbles around the nanoparticles. The use of nanosecond pulsed laser for PTT is highly selective and localized damage controllable from few nanometers to tens of micrometers depending on the laser pulse duration and particle size [23]. This makes the method useful for single metastatic cell killing and small tumor eradication. Plasmonic nanoparticles can be advantageously used to artificially enhance the optical absorption contrast between cancerous and healthy cells and to use moderate laser intensities. This way cancer cells can be heated and destroyed using a (laser) light illumination at the tumor location, at least in theory. A suitable illumination enables specific photo-damage of cancer tissues without affecting the healthy surrounding. Among available photothermal agents, plasmonic NPs are very good candidates to achieve photo-damage using moderate laser intensity. For an efficient cancer treatment following this approach, several requirements have to be fulfilled. First, gold nanoparticles have to be specifically delivered and located in cancer cells and not elsewhere in order to limit the heat generation to the malignant tissues and not to the surrounding healthy tissues. For this purpose, two approaches are usually considered to achieve specific targeting of the nanoparticles [24]

a. *Active and passive targeting*

In *passive targeting*, the nanoparticles are injected intravenously and the specific localization of the nanoparticles inside the tumor due to their rapid growth, cancer cells are endowed with vasculatures (up to 2 μm in size) that facilitate nanoparticle uptake by the cancer cells. Additionally, the lymphatic drainage of tumors is reduced compared with healthy tissues, making it harder for nanoparticles to leave the tumor once they get into it. This aspect is often referred to as the enhanced permeability and retention (EPR) effect [25]. A consequence of the EPR effect is that macromolecules or nanoparticles can accumulate in tumors at concentrations five to ten times higher than in normal tissue. In *active targeting*, the nanoparticles are also injected intravenously, but the targeting of cancer cells are achieved by coating the NP surface with antibodies, proteins or other ligands like cell surface receptors (*e.g.*, epidermal growth factor receptors, EGFRs), peptides or antibodies that have a specific binding affinity with receptors overexpressed at the membrane of cancer cells. Nanoparticle internalization can then occur by receptor-mediated endocytosis.[26]

The second aspect that has to be considered is the wavelength of the incident light used to heat the NPs. Indeed, light absorption of human tissues is minimum in the so-called transparency window (between 700 and 900 nm). Working in this region of the spectrum allows reaching tumors that can be up to several centimetres deep, along with minimum absorption and thus less heat is being delivered to the rest of the exposed tissues that are not targeted with NPs. While light absorption of spherical gold NPs peaks in the green, LSP resonances can be shifted to the infrared by using non spherical NPs. This explains why hyperthermia experiments are mainly based on the use of gold nano shells (formed by a dielectric core surrounded by a thin gold layer) [27], gold nanorods or gold nanocages, which allow accurate tuning of LSPs to the NIR spectral region. The use of spherical gold NPs can also be efficient due to agglomeration of NPs that tends to red-shift the NP absorption spectrum [28].

b. *Typical preclinical trial procedure*

First experiments on plasmonic photothermal therapy (PPTT) of cancer were made in living cells in culture. Subcutaneous tumors were grown in mice up to a certain size, typically one centimetre big. Half the mice population subsequently received gold nanoparticles via in situ deposition or via tail injection, while the remaining mice only received an injection of a saline solution, as a reference. After a few hours, most of the nanoparticles were supposed to have reached the tumor. Laser illumination was thus performed right at the tumor location for a few minutes, at a given laser intensity,

sometimes upon controlling the temperature (see Figure (b)). This process was repeated several days and at the end of the treatment, comparison was made between the mice with and without nanoparticle injection. Figure (c) shows a mouse before and after effective treatment.

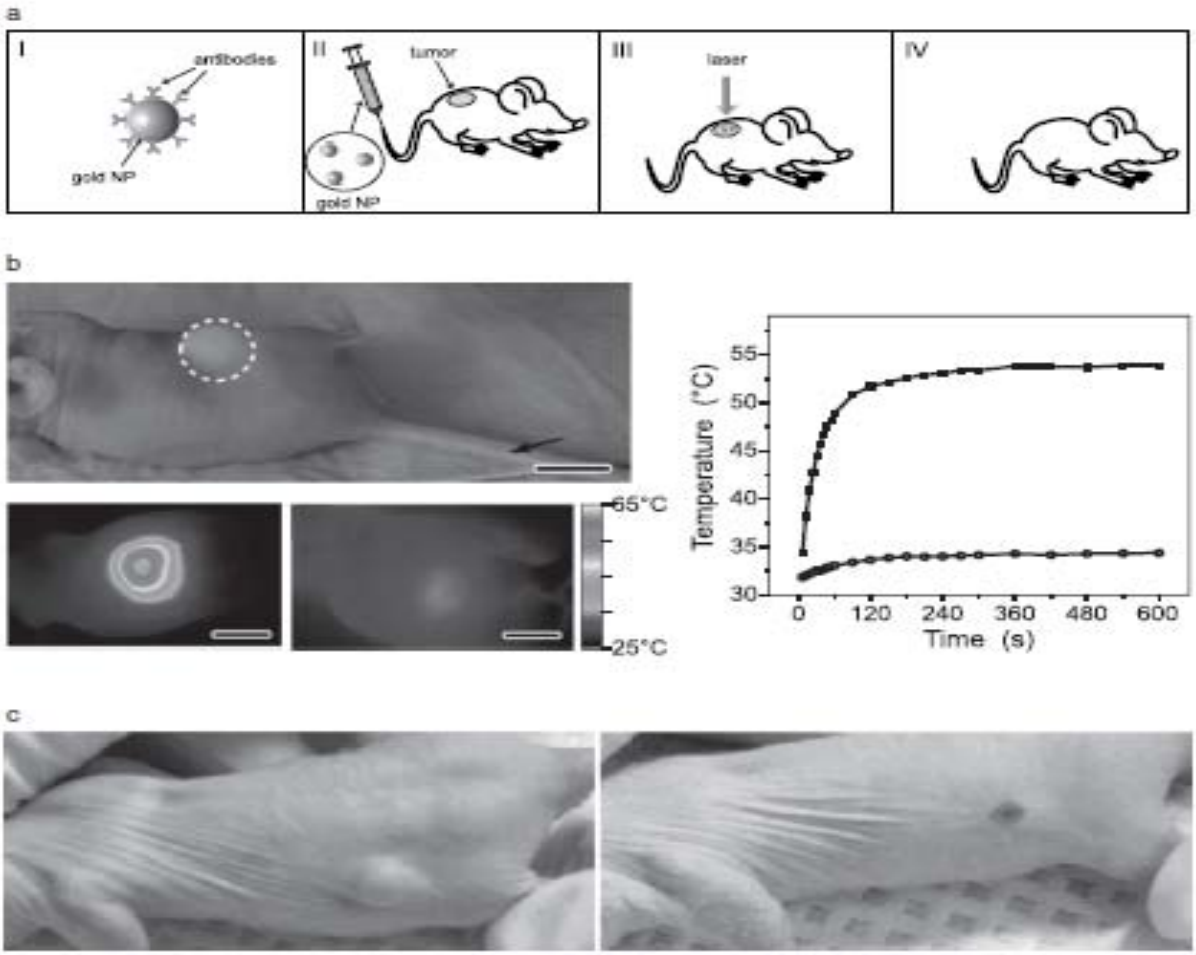

Figure (a): Schematic illustrating the usual approach in plasmonic photothermal therapy (PPTT). First, gold nanoparticles are functionalized with small molecules or antibodies that specifically target cancer cells. Then, a nanoparticle solution is directly injected into the tumor location or via tail vein injection. After a given period of incubation, the tumor is illuminated to heat the nanoparticles and generate hyperthermia. This procedure is repeated until healing is complete. Reproduced with permission from Reference [29]. Copyright 2012, WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim

(b) (Top-left) Photograph of a tumor-bearing mouse. The arrow indicates the location of injection of the nanocage or saline solutions. The dash circle indicates the size of the laser beam. (Bottom left) Thermographic images of nanocage-injected and saline-injected tumor-bearing mice. (Bottom right) Control. (Right) Plots of average temperature within the tumors (dashed circle) as a function of irradiation time. All scale bars are 1 cm. Reproduced with permission from Reference [30]. Copyright 2010, Wiley–VCH Verlag GmbH & Co. KGaA,Weinheim.

(c) Photothermal tumor ablation: (left) Mouse before treatment. (right) Mouse after treatment. Reproduced with permission from Reference [31]. Copyright 2008, American Urological Association.

b) Cell death uing photothermal mechanisms

- A simple temperature increases up to 45◦C. However, reaching a uniform temperature increase of 45◦C in all cancer cells and no deleterious temperature increase in neighbouring healthy cells may seem unrealistic. First, the precise value of 45°C is difficult to control. Then, the temperature increase cannot be restricted to the tumor volume because of heat diffusion.
- A more promising method consists in using a (nanosecond- to femtosecond-) pulsed laser illumination [31]. The sudden temperature bursts following each pulse of light remain confined at the vicinity of each nanoparticles and can reach huge values, close to 280°C, with no bubble formation. The direct consequence is the local perforation of cell membrane and destruction of organelles, leading to cell death.

- Still under pulsed illumination, a further increase of the laser power can lead to the formation of transient nanobubbles. The sudden formation and collapse of a bubble generate a shock wave that propagates through the medium and can disrupt cell membranes and lysosomes, leading to cell death [32]

c) *Plasmonic Photothermal Therapy of Atheroma*

Atheroma consists of an abnormal local accumulation of cells, lipids, and calcium in artery walls, leading to a restriction of blood flow. In most cases, atheroma most commonly results in heart attack and ensuing debility. PPTT using silica-gold nanoparticles led to significant regression of coronary atherosclerosis.

d) *Plasmonic Photothermal Therapy of Acne Vulgaris*

Used gold-coated silica nanoparticles and delivered them into sebaceous glands. By illuminating the glands using millisecond pulses of light, a local injury to sebaceous follicles and glands were performed resulting in a reduction in inflammatory lesion burden on the cheeks of patients as shown in figure.

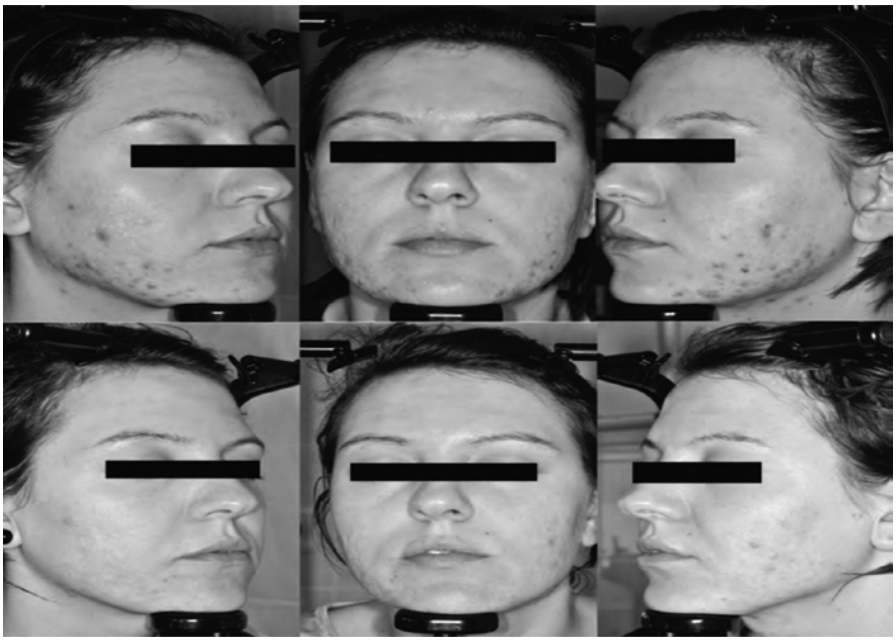

Figure: Baseline (top row) and 24-week post-baseline (bottom row) photographs of a subject showing a reduction in inflammatory lesion burden on the cheeks. Reproduced from Reference [33]. Copyright 2015, The Society for Investigative Dermatology, Inc.

e) *Drug and Gene Delivery (DGD)*

Transport and release of drugs or genes to specific location in vivo is a crucial challenge for the improvement of therapies for human diseases [34]. It focuses on targeted delivery of drugs or genes for therapeutic purposes. The principle of *plasmonic-assisted* delivery of drug or genes is that the therapeutic compounds, functionalized to the surface of metal nanoparticles, are supposed to be released only under illumination due to a temperature increase inducing a bond breakage. Investigation mainly consisted in improving this basic scheme by proposing different variants, such as the drug release from capsule-like vehicles (nanocages, liposomes, micelles). The therapeutic agents are attached to gold NPs that act as nano-carriers through the human body. Once they are at the desired location, the active agents can be detached and released by remotely heating the NPs using laser illumination [35,36]. Hence, in this kind of application, plasmonic NPs have two roles: they act as both nano-carriers and nano- sources of heat. A delivery of drugs or genes remotely triggered by an external stimulus offers strong advantages over a passive release or an internally triggered release (*e.g.*, by a chemical stimulus). The possible remote stimuli are light (ideally in the near-infrared), ultrasounds and magnetic fields. This approach allows unprecedented control of the location, the timing, the duration and the magnitude of drug release. Sufficient incident light intensity must be used to release drugs or nucleotides, but must remain below the intensity threshold causing photothermal damage of cells and tissues [37]. In particular, the timing of drug delivery could be finely adjusted. For example, insulin is most effective when delivered to a diabetic in short bursts whereas an anaesthetic should be delivered in a steady, continuous fashion [38]. Plasmonic photothermal delivery (PPTD) has been demonstrated using various geometries of plasmonic systems, such as nanospheres, nanorods, nanoshells, nanocages and liposomes. In any case, an efficient delivery system must fulfill several requirements. First, the active compounds must be protected against the surrounding

biochemical conditions during transport. Second, it must remain inactive (mute) outside the target. Third, the delivery system must be nontoxic and biodegradable if it is given parenterally.

f) Photoacoustic Imaging (PAI)

Photoacoustic imaging (optoacoustic imaging) refers to a biomedical imaging modality based on the photoacoustic effect (optoacoustic *effect*), which consists of the generation of acoustic waves produced by the absorption of pulses of light (or of radio-frequency waves in some cases). Photoacoustic (PA) (or optoacoustic) tomography combines the advantages of light and ultrasound to achieve the detection of deep tumors with high resolution (<1 mm). Photoacoustic imaging (PAI) uses optical illumination and ultrasonic detection to produce deep tissue images based on their light absorption, and uses endogenous or exogenous contrast agents. The basis of PA tomography is the generation of acoustic signals using short laser pulses. Working with NIR light ensures a maximal light penetration in tissues. The absorption of a focused pulsed laser generates a rapid and localized temperature increase (<1 °C). The subsequent thermal-induced expansion of the tissue triggers the formation and propagation of an acoustic wave (or stress wave) that can be detected at the surface of the body by using an array of ultrabroad-band acoustic transducers. Finally, a deconvolution algorithm is used to render a three-dimensional image of the absorbing tissues. This technique enables imaging in real time, with a high-spatial resolution (~ 5 μm), deep inside tissues (5–6 cm), on the anatomical functional and molecular content of biological tissues in the absence of ionizing radiation. Two main imaging modalities exist: photoacoustic microscopy and photoacoustic tomography [39]. "photoacoustic microscopy employs a coupled, focused ultrasonic detector–confocal optical illumination system to generate multidimensional tomographic images without the need for reconstruction algorithms, whereas the detectors in photoacoustic tomography scan the laser-illuminated object in a circular path and use inverse algorithms to construct three-dimensional images." Gold nanoparticles are naturally very good candidates because of their strong light absorption properties in the infrared and their biocompatibility. The use of nanoparticle-based contrast agents greatly extended PAI applications [40].

The benefit is three-fold:

(i) It allows deeper imaging within tissue with enhanced contrast. Metal nanoparticles are highly absorbing and their absorption properties can be tuned in biological transparency windows.

(ii) It allows active targeting of specific locations in living organisms using metal nanoparticles conjugated with antibodies. This way, systems endowed with weak endogenous photoacoustic contrast can be made highly visible using PAI.

(iii) PAI can be coupled with photothermal therapy using gold nanoparticles acting both as photoacoustic and photothermal agents in tumors.

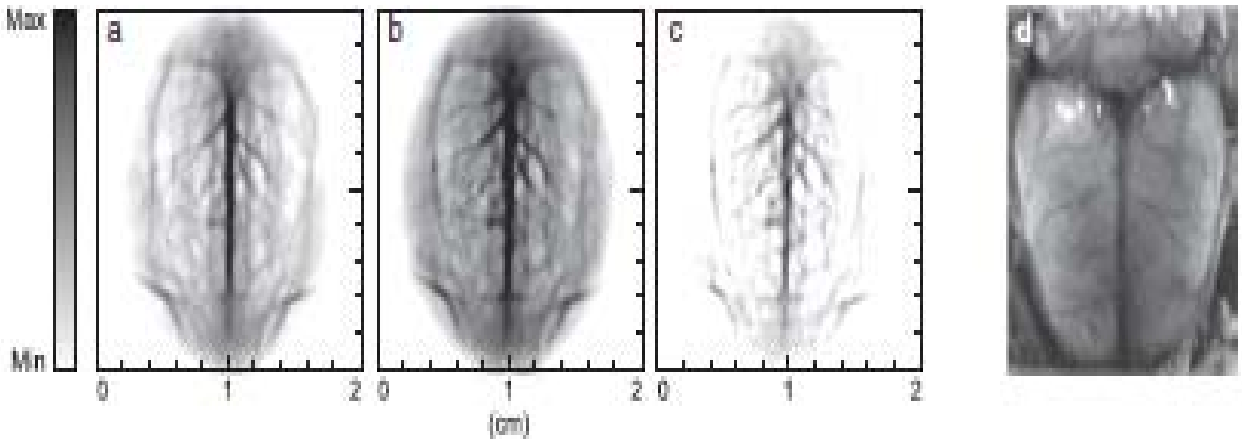

Figure: Noninvasive PAT of a rat brain in vivo employing the nanoshell contrast agent and NIR light at a wavelength of 800 nm. (a) Open-skull photograph of the rat brain cortex obtained after the data acquisition for photoacoustic tomography. (a) Photoacoustic image acquired before the administrations of nanoshells. (b) Photoacoustic image obtained 20 min after the third administration of nanoshells. (c) Differential image that was obtained by subtracting the pre-injection image (a) from the post-injection image (b). Reproduced with permission from Reference [41]. Copyright 2004, American Chemical Society.

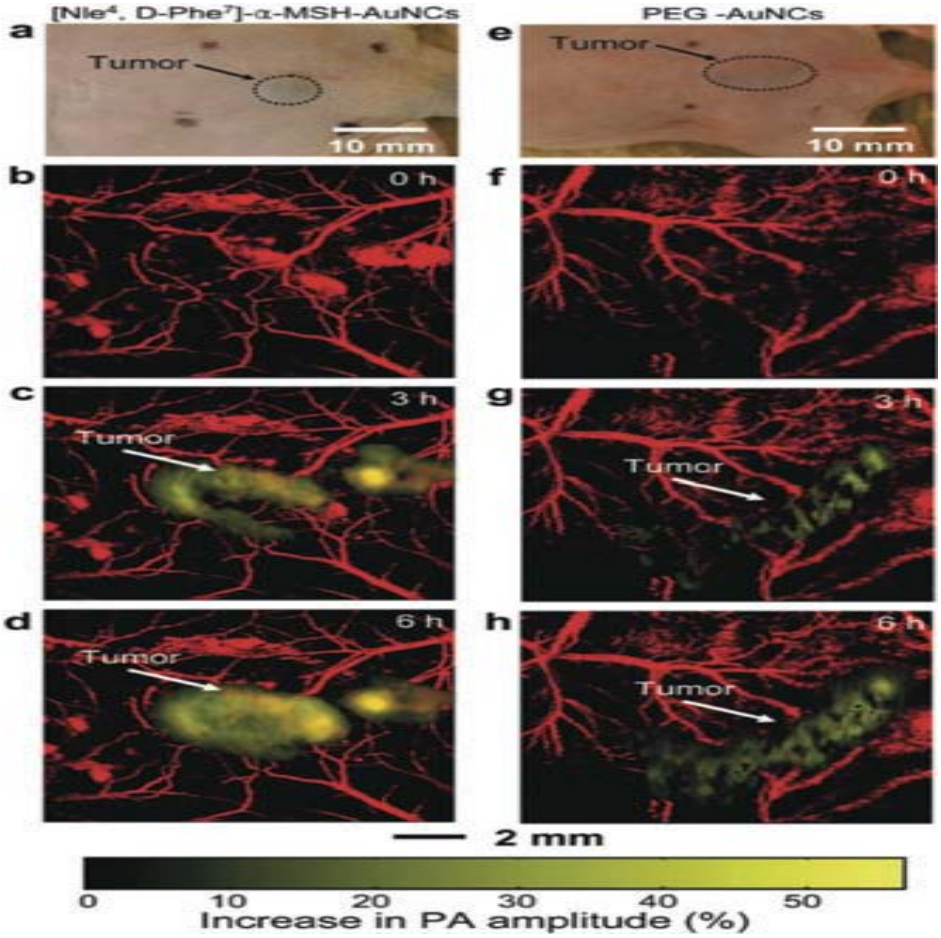

Figure: (online color at: www.lpr-journal.org) *In vivo* non-invasive PA images of B16 melanomas using gold nanocages [42]. Photographs of nude mice transplanted with B16 melanomas before injection of a) bioconjugated and e) PEGylated nanocages. PA images of the B16 melanomas after intravenous injection with 100 μl of 10 nM b–d) bioconjuated and f–h) PEGylated nanocages through the tail vein. Color scheme: red, blood vessels; yellow, increase in PA amplitude. (Reprinted with permission of ACS.)

g) Plasmonics induced nanochemistry (PINC)

Chemical reactions are influenced by various parameters such as temperature, pH and pressure. Usually, a temperature increase is accompanied by an increase in the reaction rate described by the empirical Arrhenius law that expresses the dependence on temperature T of the reaction rate constant K: $K = Ae^{-Ea/kBT}$ where A is a constant, E_a the activation energy and k_B the Boltzmann constant. The ability of plasmonic NPs to control heat over time and space with an unprecedented level of accuracy appears naturally as a means to efficiently control chemical reactions at the nanoscale. When gold nanoparticles are dispersed in a chemical reaction medium and illuminated at their plasmonic resonance, an increase of the chemical yield of the reaction can be observed. There are at least four mechanisms leading to the enhancement of chemical reaction yields in plasmonics [43]

1. The *optical near-field* enhancement in the case of photochemical reactions.
2. The local *temperature increase* due to light absorption and subsequent heat generation (named TPINC, the subject that will be developed in this section).
3. *Hot electron transfer* to surrounding oxidizing chemical species
4. A *catalytic activity* of the nanoparticle due to its nanometric size and which is not observed with its bulk counterpart [44]. Unlike the three other mechanisms, this one is not related to plasmonic properties.

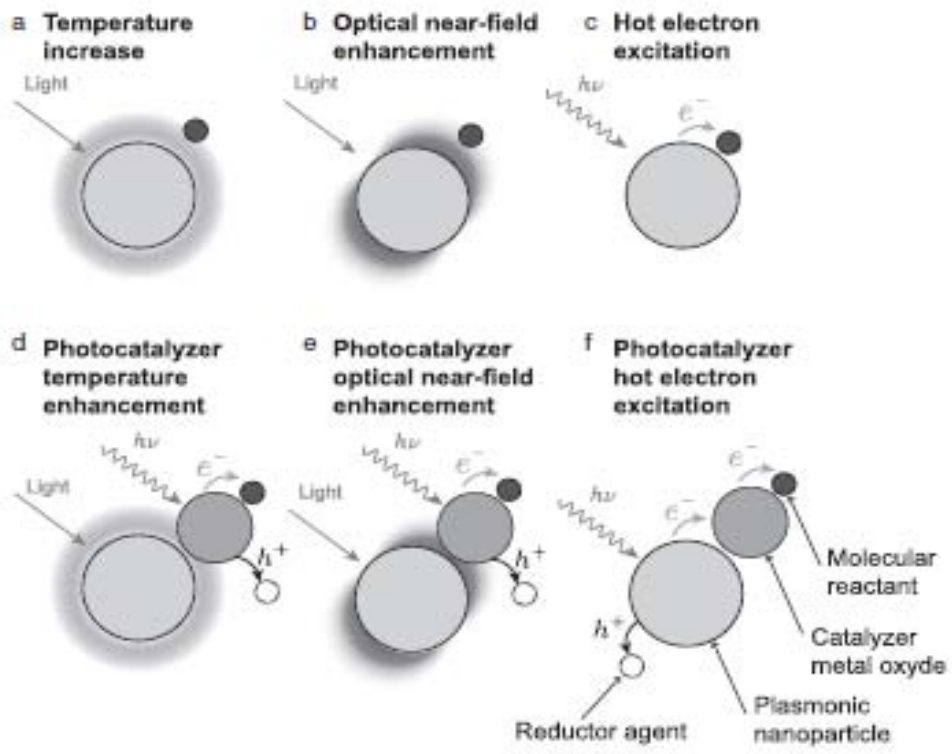

Figure: Different mechanisms proposed for enhancing a chemical reaction around plasmonic nanoparticles. Reproduced with permission from Reference [45]. Copyright 2014, Royal Society of Chemistry

The benefits of using plasmonic nanoparticles compared with the use of a regular hot plate are a priori as follows:

- Heating a small region makes it possible to make the thermal dynamics faster due to a reduced thermal inertia (typically below the microsecond timescale; In other words, it is much faster to heat (or let cool) a small volume than a large volume.
- Heating a micrometric area makes it possible to easily superheat the fluid above its boiling point (up to around 240◦C for water), with possible applications in solvothermal chemistry without using an autoclave [46].
- Heating on the nanoscale enables the formation of products with a nanometric spatial resolution.

h) Photothermal Imaging (PTI)

Photothermal microscopy enables detection of nano-objects solely based on their absorption, notably gold nanoparticles [47]. The principle is that in Photothermal Imaging (PTI) gold nanoparticles of a few nanometer big were randomly deposited on a glass substrate and immersed in surrounding medium. When these gold nanoparticles were heated by a few kelvins using a focused laser beam, which resulted in a decay of the refractive index of the surrounding medium i.e. when NP is illuminated, the temperature increase experienced by the surrounding medium induces a local variation of refractive index. This local variation of the refractive index, also known as the nanolens effect. Such a refractive index variation spreads over a distance from the particle much larger than the particle size itself, according to the thermal diffusion law. This larger volume of liquid undergoing a refractive index variation was sufficiently big to scatter an incident probe beam and make the presence of the nano-object detectable using any phase imaging technique. The good sensitivity of the technique and the stability of the signal enabled advances in nano-object spectroscopy (absorption spectroscopy and correlation spectroscopy), optical microscopy technique aimed at detecting metal NPs (10 nm) that are normally too small to be detected using any conventional optical microscopy and optical detection in living cells (localization and tracking of biomolecules and organelles).

The main interest of detecting nano-objects via absorption (and not via fluorescence, for instance) is that they behave as ideal labels: they are small enough to remain non-invasive and, more importantly, they do not suffer from photobleaching, or blinking like common fluorescent probes. Because of the absence of photobleaching, the proteins can be visualized for arbitrarily long times, offering new opportunities for efficient protein tracking in three dimensions. This is a great advantage compared with regular fluorescent markers, which tend to photo bleach very rapidly in tracking experiments. PTI is based on the detection of

phase objects. All the experimental setups are based on the use of phase imaging techniques. In any case, two laser illuminations were implemented:

- A laser beam (usually at λ = 532 nm, a few mW or less) intended to heat the nanoparticle. This laser was mechanically or acousto-optically modulated to enable a synchronous detection of the signal.
- A low-intensity laser beam (in the near-infrared) to build a phase contrast image [48].

i) Nano-surgery

Laser surgery, consists of using laser light to cut tissues, has become a reliable alternative to the conventional scalpel in fields such as ophthalmology and dermatology [49, 50]. It offers bloodless and more accurate cutting along with reduced risks of infection. At a smaller scale, laser light can be used as a tool to assist transfection of individual cells by forming a transient pore in the cell membrane [51] that permits the introduction of either therapeutic agents (proteins, DNA, RNA) or imaging agents (fluorophores, quantum dots, nanoparticles) through the cell membrane and as a tool to cut individual neurons [52].Optical transient portion in cell membranes has been demonstrated using a variety of illumination conditions, involving different mechanisms depending on the laser–cell interaction [53]. While CW illumination mainly induces a local heating at the cell membrane, femtosecond pulsed illumination with high repetition rate induces membrane permeability that is mainly the result of a low-density plasma originating from the generation of free electrons. Interestingly, this technique permits the study of one cell at a time. However, it suffers from potential photo-damage originating from the high laser power that is required. In this context, the use of plasmonic NPs makes it possible to locally increase the absorption and thus reduce the intensity requirements. Also, the possibility of controlling heating near few to single particles is expected to significantly reduce the dimension of the pore.

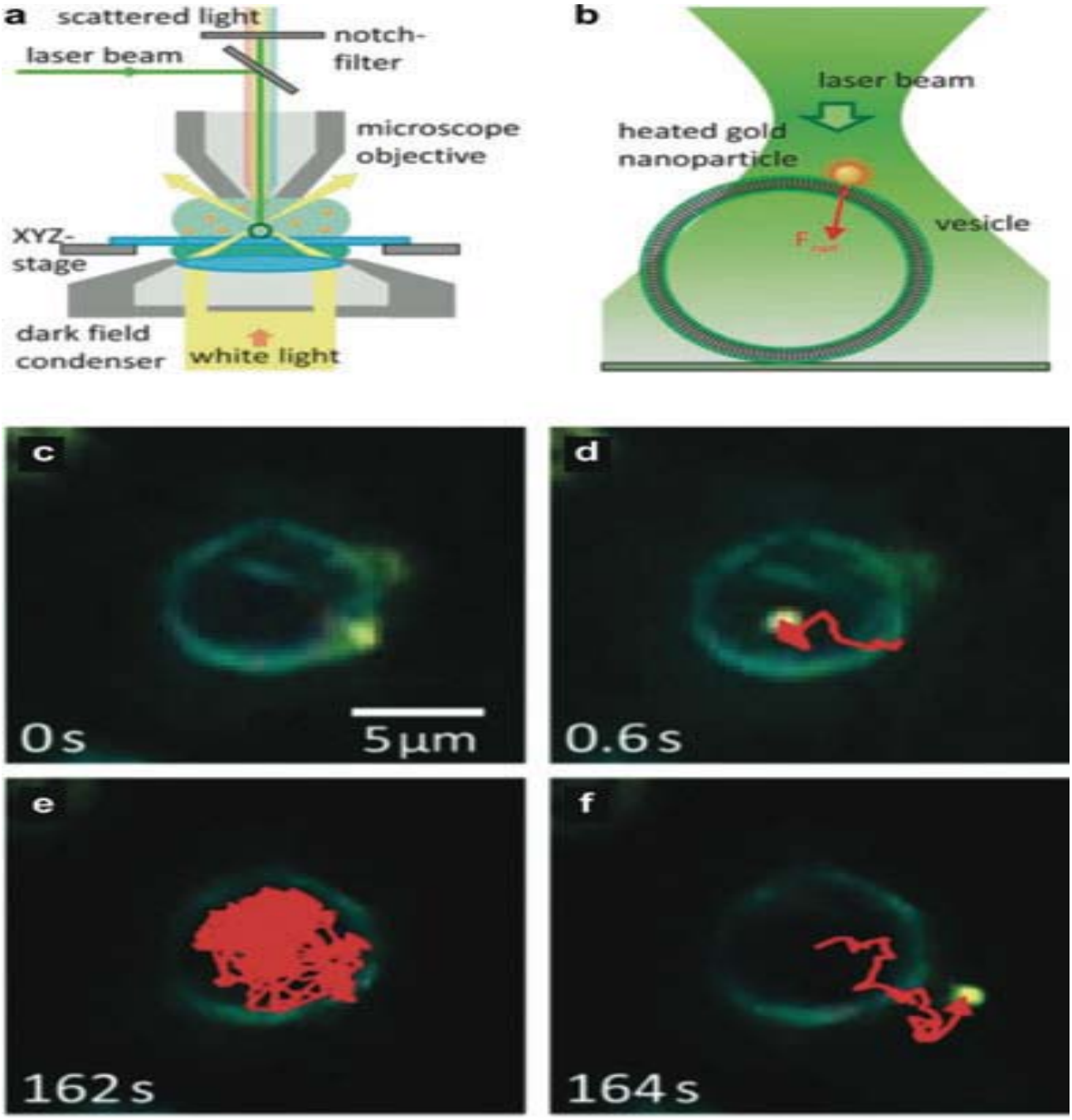

Figure: (online color at: www.lpr-journal.org) Illustration of the perforation of a phospholipid membrane using a trapped single gold NP. a) Schematic of the experimental setup used for optical injection and imaging [54]. b) Gold NPs are attached to the membrane of giant unilamellar vesicles prior to injection. The laser is defocused, resulting in a spot size of 6 µm at the focal plane of the microscope objective. c) A dipalmitoyl phosphatidylcholine vesicle before injection of a gold NP attached to the membrane. d,e) Tracking of the movement of the gold NP (red trace) shows it is confined to the inside of the vesicle. f) Often, after a certain time, the NP was observed leaving the vesicle at the same position at which it was injected. This suggests that the injection process forms a pore in the gel-phase membrane. (Reprinted with permission of ACS.)

j) Heat-Assisted Magnetic Recording (HAMR)

Magnetic recording, or magnetic storage, consists in storing binary information on a ferromagnetic film. Each bit value is spatially coded by the orientation of the magnetic dipole of ferromagnetic grains in one direction or the other (up/down or side to side). Idea is to benefit from the ability of metal nanotips to create a strong and confined optical field at its vicinity, which can be used to very locally heat the substrate over an area below the diffraction limit. In this application, it is not the temperature increase within the metal nanostructure itself that is involved in the mechanism, but rather the

optical near-field [55]. In this pioneer work, the metal structure, acting as a near-field transducer (NFT), consisted of a triangular plate endowed with a sharp beak, as represented in fig

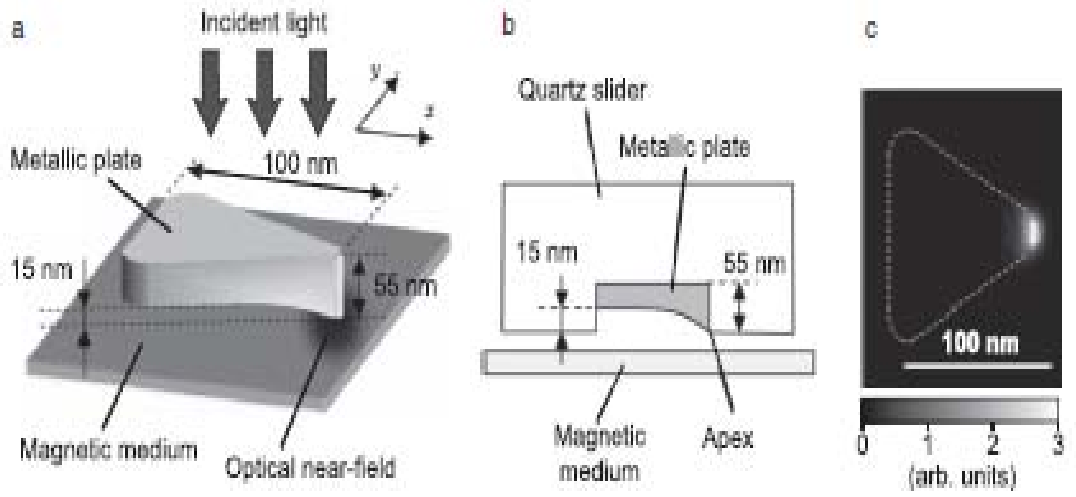

Figure: Gold is the material of choice for NFTs as it features a melting point (1064◦C) much higher than the Curie temperature of the magnetic medium in HAMR
(a) 3D view of near-field transducer (NFT)
(b) cross-sectional view
(c) Intensity distribution of the optical near-field calculated on the surface of the recording medium.
(Reproduced with permission from Reference [56]. Copyright 2006, The Optical Society)

k) Protein Denaturation: Application of Thermo-plasmonics

The thermal-induced denaturation of proteins using a pulsed laser to heat gold nanoparticles. The temporal and spatial confinement achieved when heating nanoparticles with a sub nanosecond laser could help achieve temperature as high as 470 K without boiling. The denaturation of chymotrypsin proteins within 300 ps at temperatures below 380 K. This work was carried out in the context of photothermal treatment of vessels or pigmented cells. It is that only solid-state absorbing particles (e.g., metal spheres, melanin, graphite, or iron oxide particles) can be used as such an energy acceptor for thermal micro effects. Dye molecules do probably not have the required photostability and will, therefore, rather produce photochemical damage than photothermal effects.[57]

l) Thermoplasmonics for Cell Biology

Gold nanoparticles as nanosources of heat have been proved efficient to perform local thermodynamic investigation on nanoscale and microscale biosystems, such as proteins, DNA, lipid membranes, vesicles or single living cells. This last section deals with this kind of application. In general, the state of most biosystems is highly dependent on temperature. The major drawback of such an approach is the inherent large thermal inertia. The smaller the system, the smaller the thermal inertia. For this reason, heating using a laser and an absorbing medium seems ideal. However, the main limitation of this approach is the difficulty to reliably measure a temperature distribution at the microscale. Gold nanoparticles seem ideal sources of heat: they can be designed to efficiently absorb in the infrared (a requirement to avoid phototoxicity of the high-power laser used for heating), they are biocompatible and they can lead to nano- and microscale heating, depending on the number of nanoparticles under illumination.[58]

IV. Results and Discussion

This review on applications of Gold nanoparticles as nano sources of heat provides an understanding of the interplay between optics and thermodynamics considerations and hence makes their modelling intricate. Expresses how the physical effects involved under pulsed illumination are the cause of heat generation. Also, emphasises on the small number of available thermal imaging techniques capable of probing the temperature near plasmonic structures has been drastically limited so far is now an advancing field. Discussed about the macroscopic photothermal effects such as tissue damage, fluid convection, chemical reactions or drug release. All the applications of thermo-plasmonics presented in this review feature different degrees of progress. While applications such as photothermal cancer therapy have already led to clinical trials, areas such as plasmonic-assisted nanochemistry or microfluidics are still at an early stage of development. Other promising areas of research, like

plasmon-assisted magnetic recording , phononics or thermal microbiology at the single-cell level basics are being introduced .

V. Conclusions

Here we reviewed the recent progress in the emerging and fast-growing field of thermo-plasmonics, which investigates the use of plasmonic structures as nanosources of heat. The surface-plasmon resonance-enhanced optical properties of colloidal gold nanoparticles. The plasmonic photothermal therapy of cancer is achieved by using the strongly enhanced surface-plasmon resonance absorption of gold nanospheres and nanorods. We realized that heating at the single cell level is certainly one of the future active fields of research in thermoplasmonics, favoured by the development of more efficient and reliable temperature imaging techniques Photoacoustic imaging and Photothermal imaging.

VI. Further Scope of Work

Most efforts have been devoted to trying to find i) new nanoparticle morphologies. Besides nano shells, nanospheres, nanorods, nanocages and silica-coated nanoparticles, other morphologies have been introduced such as nano prisms, stars or tripods and ii) expanding the range of applications, from cancer diagnosis to imaging of atherosclerotic plaques, brain function and image-guided therapy [60].

Remaining Current Challenges in PPTT of Cancer: The fact that the results of the clinical trials on cancer therapy have not been communicated may be a sign that the targeted challenge is bigger than expected, and may be out of reach.

Restriction to subcutaneous tumors: Preclinical trials have been successfully conducted only on *subcutaneous* tumors, *i.e.*, tumors that are easily accessible, removable using simple surgery, and that do not need therapy.

Temperature spreading: Many approaches are based on a global photothermal effect under cw illumination. In such a case, the spatial distribution of the temperature will not be localized around each nanoparticle but rather delocalized throughout the whole tumor

Temperature nonuniformity: Another problem occurs under cw illumination. There is no reason for the nanoparticle distribution to be uniform in the tumor.

Temperature monitoring: Ideally, to make sure any part of the tumor reaches the desired temperature and no injury are caused to nearby organs, a three-dimensional map of the temperature increase would be required. But no imaging technique enables this performance, except MRI.

Opacity of human body: The human body is not transparent. This explains why magnetothermal treatments have reached phase-II clinical trials in PPTT approaches (human body is fully "transparent" to magnetic fields). Even in the infrared, it is difficult to reach a light penetration larger than one centimetre, not only because of water and blood absorption [59], but also due to tissue scattering.

Remaining Issues in Near-Field Assisted HAMR: One of the major problems is the heat generation within the metal near-field transducer Itself. One can hardly imagine that NFT could heat up a neighbouring solid via its near-field, while remaining cold. Gold nanoparticles are known to reshape at temperatures much weaker than the melting point of gold. The lifetime of the NFT may suffer from this problem. For this reason, efforts are made to find new materials in plasmonics that can sustain higher temperatures, such as metal nitrides (TiN, ZrN) or refractory metals (W, Mo). TiN and ZrN have been shown promising as their plasmonic resonance are similar to gold's resonance (in wavelength and magnitude), and because they feature melting points close to 3000◦C. However, they are not supposed to be good near-field enhancers [61]

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