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Applications of nanomaterials in modern medicine

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Abstract Nanomaterials represent a class of materials based on nanoscale structures. Nanomaterials are currently used in a wide variety of applications, including, optoelectronics, energy conversion, biology health care and medicine. Among different types of nanomaterials, gold nanoparticles have received considerable attention in disease diagnosis and therapy due to their optical and chemical properties (Liz-Marzan in Mater Today 7:26–31, 2004). This paper reports the main optical and photo-thermal properties of gold nanoparticles. Particularly, we show that gold nanorods embedded in cholesteric liquid crystals demonstrate to control the "selective reflection" of a light beam. Investigation of the optical properties of the obtained material reveals an original and efficient tool to detect temperature variations at the nanoscale useful for photo-thermal based therapies applications. Finally, the concept of 'nanoparticle-protein corona interaction can be exploited for application ranging from regenerative medicine to theranostics.

Keywords Nanomaterials · Plasmonics · Photo-thermal therapy · Nanomedicine

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1 Introduction

Nanotechnology is based on understanding and control of matter at the nanoscale, at dimension ranging between approximately 1 and 100 nm. Nanotechnology is gaining importance in modern biology and medicine due to its function at small size and the ability to achieve targeted effects. Nanoscale device are approximately 1000 times smaller than human cells. Due to their small size and larger surface area relative to their volume, nanoscale device can easily interact with biomolecules (e.g., enzymes, proteins) both at surface and inside cell. Due to these peculiar characteristics, nanoparticles (NPs) have the extraordinary capability to detect diseases at the micro level and deliver treatment. Gold NPs (GNPs) are an attractive class of nanomaterials, as they allow confining light at the nanoscale crossing light diffraction limit by exploiting localized plasmonic resonance (LPR) (Liz-Marzan 2004). Under a resonant light illumination, GNPs are able to convert light into heat, thus becoming nanosources of heat and opening up an unpredictable number of applications, ranging from photonics to nanomedicine (Govorov and Richardson 2007). This phenomenon can occur as the absorption associated to the LPR can trigger heat generation process that involves not only absorption of incident photons, but also heat transfer from the metallic nanoparticles to the surrounding medium. Historically, the photo-thermal properties of GNPs have been considered a side effect in plasmonic studies since these have been typically focused on the merely optical and spectroscopical properties of plasmonic NPs. Scientists have only recently realized that this effect, which can turn metal NPs into nanosized sources of heat remotely controllable using light, provides an unprecedented way to control thermal-induced phenomena at the nanoscale (Baffou and Quidant 2013). Moreover, such GNPs have also a large technological potential in sensing and energy-harvesting applications as well as in medical domains, in gene therapy and as active elements in photothermal therapy (Prashant et al. 2007). Among the various applications of NPs, healthcare is considered one of the most significant fields (Jhal et al. 2014). This field has witnessed an outburst of the nanotechnology research, which has lead, among the others, to deeply modernized drug delivery strategies, which have allowed transport of a wide variety of biologically active molecules. NPs increase dispersibility and in vivo stability, support passive and active targeting, minimize side effects and enable a superior therapeutic index. Due to their high surface area to volume ratio, NPs can transport high-dose therapeutic and diagnostic payloads, which are protected from interaction with the environment until delivery at the target site, thus providing for an efficient, local theranostic effect. For all these reasons, NPs have the potential to revolutionize the treatment of many disorders such as cancer (Duncan and Gaspar 2011; Nazir et al. 2014; Saenz del Burgo et al. 2014), cardiovascular diseases (Zhaorigetu et al. 2014), type-1 diabetes (Domínguez et al. 2014), fungal infections (Yang et al. 2014), lymphomas or leukaemia (Babar et al. 2012), as well as disease management in poorly accessible compartments of the body such as brain (Haque et al. 2014) and eye (Cattaneo et al. 2014; Kobayashi et al. 2014). Critical conditions arise when NPs come into contact with a physiological environment, such as the human blood (Walkey and Chan 2012). They are instantly surrounded by high concentrations of free protein (e.g., more than 3700 identified proteins are present in plasma) driven either by a potential energy gradient, or just by diffusion, both these mechanisms resulting in a fast (<1 min) formation of a protein layer at the nanomaterial surface. Recently, Dawson and coworkers introduced the concept of the 'nanoparticle-protein corona' (Cedervall et al. 2007). The word corona means 'crown' in Latin and is the astronomical term used to describe the aura of plasma surrounding the Sun. Similarly, the proteins interacting with a NP can be thought to form an aura that surrounds it, being this phenomenon dubbed 'protein corona'. Although the concept of proteins interacting with nanomaterials was not new (Diederichs 1996; Lück et al. 1998), Dawson et al. were the first to recognize that the blood proteins could be seen as forming a more dynamic 'corona', rather than a solid fixed protein layer.

This paper, reporting on the main optical and photothermal properties of GNPs, describes some recent efforts to use them in a number of research fields, and in particular in modern medicine. In particular, we describe the experimental methods that have been developed to detect nanoscale temperature variations under a suitable optical illumination. Finally, we overview the bio-nano-interactions faced by nanomaterials in a physiological environment.

2 Photo-thermal effects in plasmonic NPs

Hyperthermia is a class of medical treatment based on exposure of body tissues to temperatures slightly higher than the physiological one (above 40 °C) to damage and kill cancer cells. Such a treatment has been exploited at a preclinical level in combination with radiation therapy (Wust et al. 2002). Hyperthermia exploits the lower thermal tolerance of cancer cells due to their reduced blood supply. Hyperthermic treatments using commercially available instruments are often limited to shallow penetration depths (<3 cm), low treatment temperatures, and regions of the body with regular surface composition. Invasive approaches using microwave antennas are highly

susceptible to interference, while magnetic particle treatments require large doses. Photo-thermal therapy is a minimally invasive method in which photon energy is converted to thermal energy sufficient to induce cellular hyperthermia. To obtain a selective illumination and, consequently, a confined heating, it is possible to combine a focused beam (CW or pulsed) or even a fiber optic (invasive approach) and administration of photoactive molecules or NPs. Photoexcitation of such molecules or NPs results in non-radiative relaxation and local heat transfer to the surrounding tumor environment. In the last 10 years, GNPs have demonstrated a remarkable breakthrough in fighting cancer through the exploitation of the LPR mechanism. GNPs can be injected into the bloodstream and accumulate at tumor sites, where they heat the local environment upon irradiation with laser light at wavelength corresponding to the LPR of the NPs. Consequently, adjacent healthy tissues, which are free from GNPs, are not affected by the bare laser irradiation. Only cancer cells in the direct vicinity of the GNPs can undergo hyperthermia, and, as a result, death, thus providing a novel "drug-free" cancer therapy, namely plasmonic photothermal therapy (PPTT) (Huang et al. 2008). In such cancer therapy applications, GNPs are very good candidate due to their enhanced absorption cross section, which is four to five orders of magnitude larger than conventional photo absorbing dyes. In addition, a suitable nanosystem which is effectively able to be associated to biological structures needs also to take into account the requirement of a LPR of GNPs as close as possible to a water transparency window (700–900 nm), where tissue absorption is low and the penetration depth of the radiation is high (Fig. 1). In the inset of Fig. 1, blue, green and red, respectively, 5 mW laser beams are placed on human fingers to visually check how much light can be transmitted through a roughly 1 cm thick finger. Red laser light can be seen passing through the tissue, while green and blue laser light are absorbed by the tissue and converted to heat energy. This observation can be confirmed by considering the absorption spectrum of a human hand (Fig. 1). For effective photothermal therapy, various photothermal agents, including aggregated GNPs, gold nanoshells, gold nanocages and gold nanorods (GNRs) have been applied in vitro and in vivo, so far. Remarkable, GNRs have been shown the most suited class of GNPs in absorbing NIR radiation and converting it into heat, being at least six times more efficient in this task than gold nanospheres or nanoshells. GNRs are also particularly advantageous due to their efficient large scale synthesis, easy functionalization and colloidal stability. Indeed, upon NIR light irradiation of GNRs, the largely absorbed radiation can be efficiently converted into heat, as the excited conduction band electrons decay to the ground state by releasing their energy. The use of NIR absorbing materials has merits such as maximal penetration of light, up to 10 cm, due to relatively lower scattering and absorption from the intrinsic tissue chromophores. The photo-thermal efficiency of GNRs is $\mu = \sigma_{abs}/\sigma_{ext}$ where σ_{abs} is the absorption cross section while σ_{ext} is the extinction cross section ($\sigma_{ext} = \sigma_{abs} + \sigma_{sca}$; σ_{sca} is the scattering cross section). It is easy to prove that for small GNRs (long axis less than 30 nm) $\mu \approx 1$ since σ_{sca} is almost negligible and for this reason GNRs can convert almost 100 % of the impinging NIR light to heat.

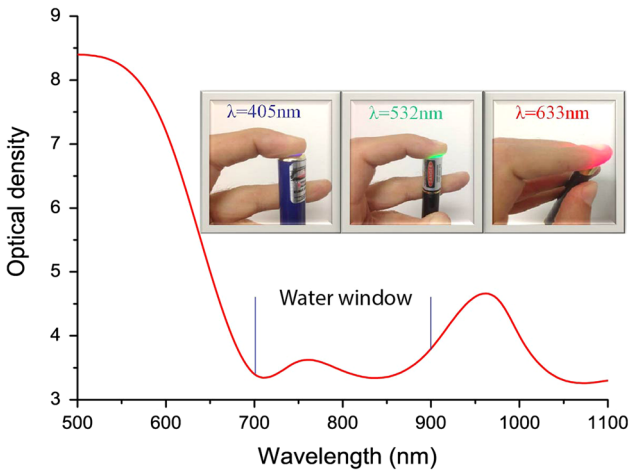

Fig. 1 Absorption spectrum of a human hand along with the propagation of visible light in living tissue (*inset*) (color figure online)

3 Plasmonic based thermometer

A strong limitation to the application of GNPs for hyperthermia is given by the possible cell death, at temperatures above 42 °C, also in the healthy tissues surrounding the tumor site (Wust et al. 2002). The risk of damaging healthy tissue is a serious drawback, therefore the ability of measuring the local temperature of the illuminated area with high sensitivity (less than 0.5 °C) is required. Monitoring temperature variations in a sample undergoing optical illumination represents a relevant issue, not only in nanomedicine but also for photonics and plasmonics. Direct temperature measurement has been made by using thermal camera analysis. However, despite its high sensitivity ($\approx$0.2 °C), the technique possesses a limited spatial resolution (10–15 μm), thus enabling measurement of the temperature only at surface (Baffou et al. 2012). Other approaches, based on the possibility to combine GNPs and phase transitions (due to the induced photo-heating), require incorporation of GNPs in ice (Richardson et al. 2006), or use of GNP suspensions in suitable fluids (Wilson et al. 2002). None of above techniques, however, can combine the advantages of reliability, fast read-out rate and

high-resolution, thus presenting still limitations to their utility for nanoscale temperature monitoring. In this framework, we have advanced a step-forward in the monitoring nanoscale temperature variations under optical illumination by combining GNRs properties and thermotropic cholesteric liquid crystals (CLCs) capabilities (De Sio et al. 2013). Compared to previously employed techniques, the reported method represents an innovative and non-invasive tool that takes advantage of the properties of well known materials, like CLCs, for a continuous, careful and highly sensitive monitoring of photoinduced temperature variations around GNRs.

To this purpose, cetyltrimethylammonium bromide (CTAB) capped and water dispersible GNRs have been synthesized (Placido et al. 2009) and subsequently transferred in chloroform, to obtain a dispersing medium with LCs. The transmission electron microscopy image of Fig. 2a indicates that the particle population consists mainly of GNRs with a 2.5 ± 0.4 aspect ratio (AR) while the normalized UV–Vis absorption spectrum of GNRs solution is shown in Fig. 2b. The GNRs dispersion exhibits two typical plasmon bands: a transverse band at 520 nm and a longitudinal one at 674 nm. Subsequently, 10 μm thick glass cells have been filled at room temperature by capillary action with a homogeneous dispersion of GNRs (7 wt %) in CLC (helix pitch of about 400 nm). Figure 2c shows a polarized optical microscope (POM) view of a sample, where the presence of declinations is quite clear. This kind of structural defects, called "oily streaks", appear as long bands that divide the ideal domains of the layers. Oily streaks are markers of a lamellar phase and clearly indicate the existence of a Grandjean texture (that means CLC helices oriented perpendicular to cell surface) of the CLC configuration. We have analyzed the spectral reflection properties of the CLC configuration by probing it with a white light source under the optical illumination due to a CW NIR pump laser emitting at $\lambda = 680$ nm ($P_{\text{pump}} = 0.2$ W/cm^2) in the high absorption range of the GNRs (longitudinal band). Figure 2d reports the behavior of the CLC reflection band under illumination with the pump beam, for different exposure times (from 0 s up to 45 s). The CLC acts as a mirror for all the wavelengths within the reflection band of the impinging white light, which are back reflected. By optically pumping the same sample area, the photoexcitation of GNRs induces a conversion of light to heat; therefore, the system cool down by exchanging energy with the CLC. Figure 2d clearly presents that, by keeping constant the pump power and increasing the exposure time, a linear red shift ($\approx$25 nm) and a suppression of the reflection band take place, due to a gradual enhancement of the local temperature. To validate the effect of the GNR-induced local heating on the CLC optical response (see De Sio et al. 2013 for details), we have performed a control experiment by varying the

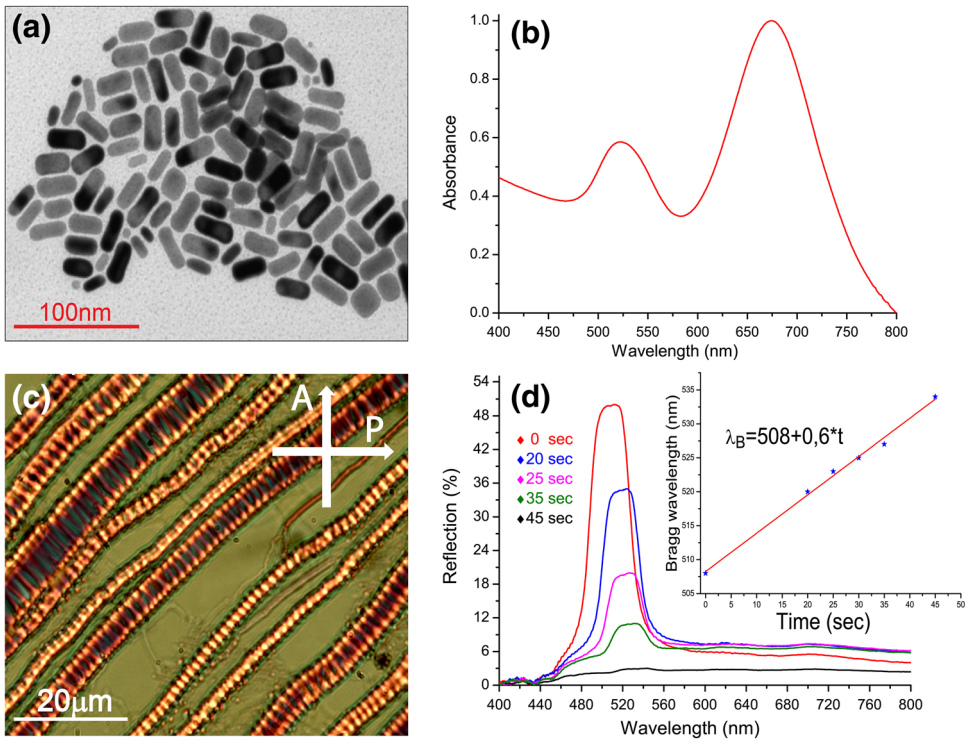

Fig. 2 TEM image of chloroform dispersed GNRs (**a**) along with the normalized UV–Vis absorption spectrum (**b**). POM view of the sample (**c**) and its reflection spectrum for different values of the illumination time (**d**). In the *inset* of (**d**) is reported the linear fit of the position of the center of the reflection band versus the time (color figure online)

sample temperature (T) from 25 °C up to 65 °C and monitoring the reflection band behavior; once again, we have observed the same linear behavior (the calibration function is $\lambda_B = 494 + 0.64 * T$) which clearly confirms that the behavior reported in Fig. 2d is due to a photothermal mechanism (the two calibration functions exhibit, within the experimental error, the same linear behavior). This result shows that it is possible to measure the temperature around GNRs, at a given illumination time, by simple measuring λ_B with a sensitivity of about 0.03 °C.

4 Nanomaterials in physiological environments: challenges and opportunities for the life sciences

In a physiological environment (e.g., the blood) nanomaterials acquire a new identity, named biological identity, which is characterized by size, surface charge, and aggregation state, along with the thickness, density and composition of the protein corona. It is noteworthy that the nanomaterials biological identity is dramatically different from the synthetic identity (size, shape, and surface chemistry post-synthesis) formerly designed in the lab. The new biological identity affects the physiological response of nanomaterials in a physiological environment controlling relevant biological processes such as complement activation, immune response, coagulation and thrombosis (Fig. 3). This was first shown for opsonin-coated nanocarriers. An opsonin is a molecule that enhances phagocytosis by marking an antigen—in this case the nanocarrier—for an immune response. Coverage of opsonin-coated nanocarriers' surface with elements of complement and, successively, with immunoglobulins (Igs) results in "opsonization". This is the removal of the opsonin-coated nanomaterial from blood circulation by macrophage-mediated transportation to the liver and spleen, where the nanocarriers are metabolized. Opsonization is not the only concern for nanomaterials in a physiological environment. Among unwanted effects, the protein corona dramatically influences the targeting ability of functionalized nanomaterials. At present day, active targeting is believed the most suitable approach for accelerating the use of nanomaterials towards clinical application (Yu et al. 2010). Active targeting exploits the receptor profiles of target cells by targeting moiety (e.g., ligand) incorporation that simplifies the delivery at, and entry of a payload in target cells by a receptor-mediated mechanism. Unfortunately, upon formation of the protein corona, surface ligand-receptor recognition may be totally hidden. Nonetheless, proteins that are not recognized by any receptor on the cell will make the particle less attractive to the cell. A way of disabling opsonization and preserving the surface functionality consists in coating the surface of the nanomaterial with hydrophilic moieties such as polyethylene glycol (PEG) and/or other copolymers that are able to prevent such phenomenon by hiding the nanomaterial from macrophage uptake and allowing them to stay in blood stream for a long time. However, PEGylation

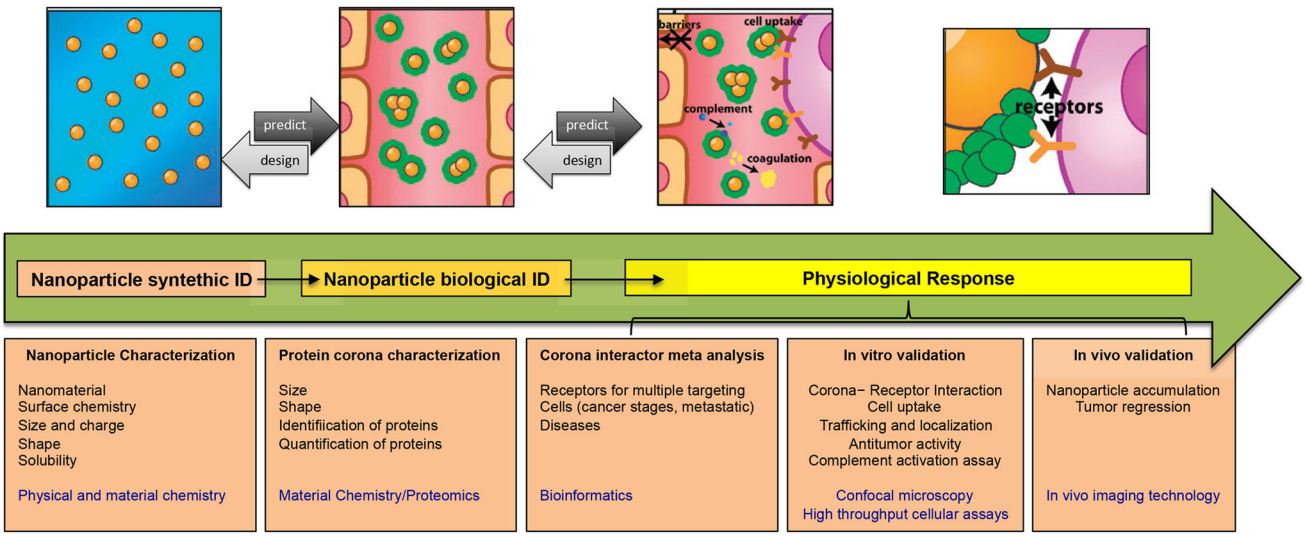

Fig. 3 Relationship between the synthetic identity, the biological identity and the physiological response of a nanomaterial in a physiological environment. Nanomaterials are synthesized with a distinct synthetic identity (ID). When covered by a "protein corona" in vivo, a new particle biological ID emerges that is ultimately responsible for the physiological response (e.g., exposed epitopes of proteins in the corona are not recognized by the corresponding receptor). In the *boxes* the main steps of particle characterization are shown. Within each *box*, the kind of information, the most frequently employed validation assays and the interacting fields of research (in blue) are indicated. Adapted with permission from (Walkey and Chan 2012) (color figure online)

only reduces the amount of recruited proteins, but it does not totally prevent protein binding (Pozzi et al. 2014). Thus, the scientific community believes these tightly associated proteins represent the interface that is actually "seen" and "read" by living organisms. In other words, what target cells really process is not the bare nanomaterial, but rather the complex made of the nanomaterial and its "protein corona". This evidently shows that, at cellular level, cell-nanomaterials interactions are not mainly dependent on the bulk composition of the nanomaterial or on its surface functionalization but somewhat on the identity, arrangement and residence time of the proteins at the particle surface. The last trend in the field is to exploit the protein corona in a beneficial way. A clear example is given by the so-called 'protein corona effect' for targeted drug delivery. The basic idea is that the protein corona could include proteins engaged from the blood that could let the NP to interact with specific receptors expressed on the plasma membrane of target cells (Fig. 3). This means that a long-standing corona with receptor-binding sites could associate with the target cell long enough to activate endocytosis and intracellular cargo delivery. To consolidate such a targeting strategy researchers should be able to design nanomaterials capable of capturing plasma proteins that could be recognized by receptors of target cells. Evidently, two main requirements can be identified: (1) understanding which plasma proteins effectively deliver particles to which location and (2) identifying those proteins with the highest affinity for lipid surfaces of different compositions or surface characteristics. Even when binding to specific receptors is achieved, a different trafficking and final localization of the targeted NPs can be obtained, compared to that of the bare ligand, and that desired by the targeting procedure. Consequently, in this perspective, the NP-protein corona (besides size and shape of the structure) is indeed responsible of the final subcellular location of a specific NP upon interaction with a cell and, thereby, the range of disease processes that the NP can access. Therefore, in the future nanomaterials could be classified in terms of their biomolecule corona, which mediates their interaction with cellular machinery. Once fully mapped, the relationships between synthetic identity, biological identity, and corona-mediated physiological response will enable researchers to predict the behavior of nanomaterials in a physiological environment. This would represent a new paradigm in the field of nanoscale toxicology, and in the design of nanomaterials for the life sciences. In the near future, the emerging field of nanomaterial-protein corona research is expected to rapidly evolve from basic, descriptive research to applicable knowledge and technologies for implementation in many fields such as drug improvement and drug development, regenerative medicine and theranostics.

5 Conclusion

We have reported on the main optical and photo-thermal properties of GNPs. In particular, by combining the plasmonic photo-thermal conversion of GNRs and the thermosensitivity of chiral liquid crystalline materials (CLCs), an all-optical control of the selective reflection of the CLC has been obtained. It turns out that the ingenious combination of plasmonic nanomaterials (GNRs) and self-organized soft-matter (CLC) allows the realization of a smart method for detecting the temperature variation around GNRs under optical illumination with very high sensitivity. The overall results open-up the venue for realizing a new generation of tools for nanomedicine and plasmonic thermal based therapies. Finally, we have proposed a general overview of the main results obtained in the field of nanomaterials-protein corona interaction in physiological environment.

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