AuNPs

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Gold nanoparticles (AuNPs) have gained high prominence in the biomedicine field, due to their own physico-chemical properties that are suitable for different imaging or therapeutic uses, versatile structural modification, including easy functionalization of their surface with different chemical entities (e.g., chelators, targeting biomolecules or cytotoxic drugs), favourable biological half-life, low toxicity and biocompatibility. In particular, the use of AuNPs in radiopharmaceutical development has provided various nanometric platforms for the delivery of medically relevant radioisotopes for SPECT/PET diagnosis and/or radionuclide therapy

nanomedicine gold nanoparticles nuclear imaging radionuclide therapy

1. Introduction

Nanotechnology is a discipline of science and engineering that has led to innovative approaches in many areas of medicine based on the use of biocompatible nanoparticles. Its applications in the screening, diagnosis, and treatment of disease are collectively referred to as “nanomedicine”, an emerging field that has demonstrated great potential to revolutionize individual and population wide health in the future. It can be seen as a refinement of molecular medicine, integrating innovations in genomics and proteomics on the path to a more personalized medicine [1][2].

For biomedical applications, nanoparticles can be obtained with a wide variety of materials including inorganic compounds or organic polymers, among others. The use of different materials provides nanoparticles of different sizes and shapes with varied physico-chemical properties well-fitted for a specific use in biomedicine [3]. In this respect, it is important to have in mind the influence of surface and quantum effects that affect the chemical reactivity of nanosized materials, as well as their mechanical, optical, electric and magnetic properties [4][5].

The biological fate and potential toxicity of nanoparticles are also crucial issues, which might restrict their use for medical applications. In fact, for some of them (e.g., quantum dots), their inherent toxicity is a potential drawback but for many others (e.g., iron oxide and AuNPs) toxicity issues are less relevant. Nanoparticle biodistribution can vary greatly depending on the type and size of the particle, as well as on their surface chemistry [6][7]. For imaging and/or therapy of cancer, the selective delivery of drugs or radionuclides into the tumour tissues is of paramount importance. For this purpose, nanoparticles offer unique advantages. In fact, many NPs undergo the enhanced permeability and retention (EPR) effect that is involved in the passive targeting of leaky tumour tissues. The EPR effect is a result of the leakiness of the newly forming blood vessels and poor lymphatic drainage in growing tumours. During the angiogenesis process, the endothelial cells from the blood vessel walls do not seal tightly

against each other, leaving fenestrations of approximately 200–800 nm in diameter. These processes lead to a passive accumulation of nanoparticles in tumour tissues, as shown in Figure 1 [8]. On the other side, the versatile functionalization of the NPs surface with targeting biomolecules (e.g., a peptide or an antibody) allows the specific targeting of tumours through interaction with receptors overexpressed in the tumour cells or in the tumour microenvironment (Figure 1) [9][10][11].

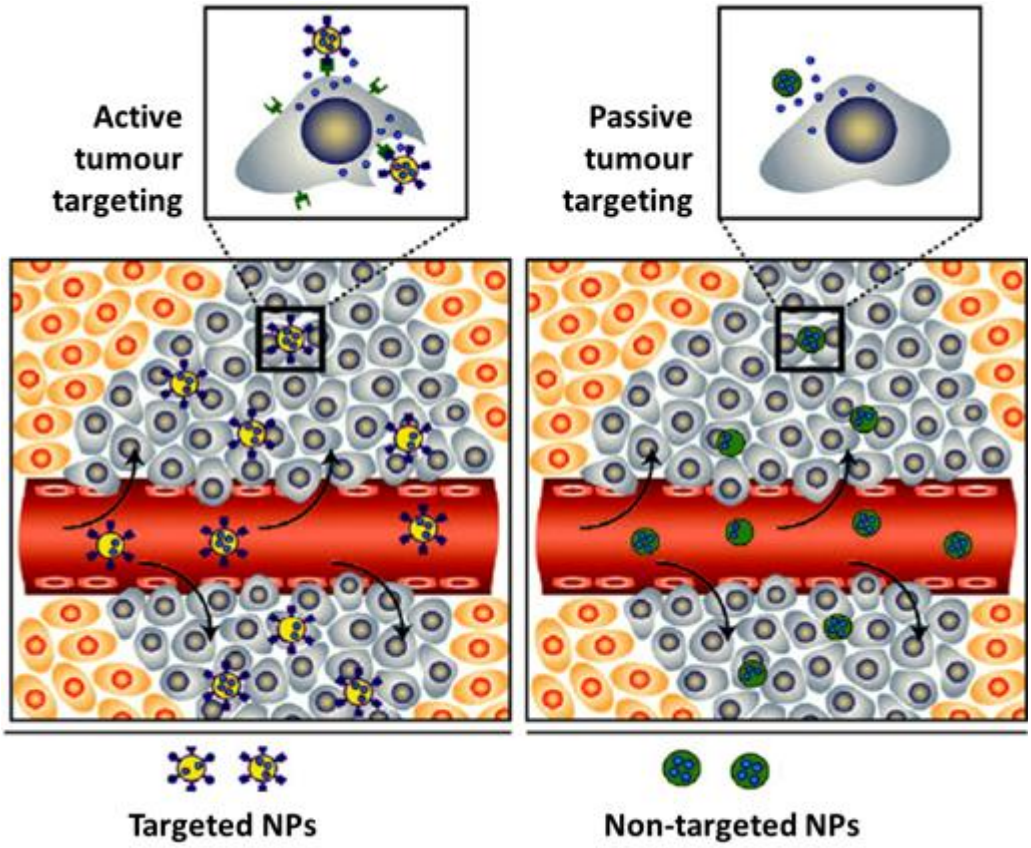

Figure 1. Illustration of the accumulation of nanoparticles in tumour tissues: passive vs active targeting. Adapted from Mahmoudi et al. (2011) [12].

For biomedical applications, namely for cancer imaging and therapy, AuNPs offer the possibility of a versatile functionalization with targeting biomolecules for specific accumulation in tumour tissues, allowing more precise diagnostics and/or localized therapeutic effects. For instance, the combination of nuclear medicine modalities with nanotechnology offers unique opportunities to achieve this goal by allowing the easy and convenient merge of a variety of diagnostic and therapeutic capabilities into a single agent, within a theranostic approach of cancer. This requires the design of radiolabeled nanoconstructs that can be tailored ideally to the needs of every patient by selecting the appropriate nanoparticle, targeting biomolecule and imaging or therapeutic radionuclide [13][14][15]. Moreover, there are currently available different methods to manipulate the size and shape of gold nanoparticles, spanning from shapes like nanospheres (or nanoshells), nanorods, nanocages to nanostars (Figure 2), to obtain AuNPs tailored to the different biomedical uses [16][17].

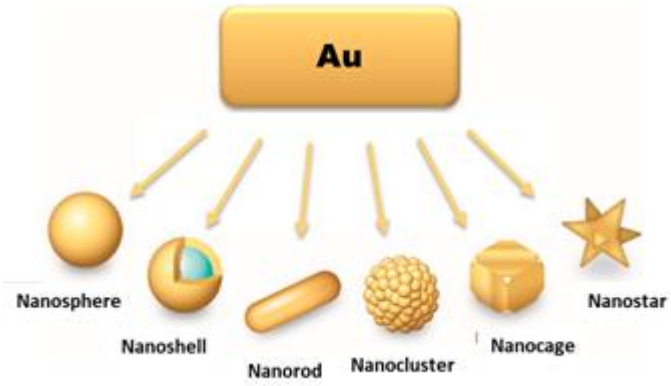

Figure 2. Different types of AuNPs, according to their shape and morphology. Adapted from L. F. de Freitas et al. (2018) [18].

2. Synthesis of Gold Nanoparticles

One of the most common methods of AuNP synthesis is by reduction of a gold precursor, generally the tetrachloroauric acid ($HAuCl_4$), in the presence of a stabilizing agent (Figure 3a). In order to guarantee the reduction of the gold, strong to mild reducing agents are used, like $NaBH_4$, hydrazine or citrate. In 1951, Turkevitch et al. developed one of the most conventional synthetic routes, still in use to this day, which consists on the reduction of Au(III) in $HAuCl_4$ by citrate in water. It is known as the citrate reduction method, which allows the formation of citrate stabilized AuNPs and a controlled size of the particles by varying the citrate/gold ratio [19]. A few years later, in 1994, Brust et al. introduced a new procedure for the efficient synthesis of stable AuNPs with reduced dispersity and controlled size, which represented at the time an important breakthrough. This procedure is based on the use of thiolated ligands that strongly bind to gold due to the soft character of both Au and S. After addition of a reducing agent ($NaBH_4$), the Au(III) is reduced to Au(I) and the AuNPs are formed [20]. This opened the opportunity to develop AuNPs using a great variety of thiolated ligands. This method allows the control of core nanoparticle size by shifting the ratio of thiol/Au in the reaction mixture; for instance, the use of larger thiol/Au ratios affords smaller core sizes with less polydispersity [21][22].

In recent years there has been an increased interest on green methodologies for the synthesis of AuNPs, using alternative reducing agents to $NaBH_4$ or hydrazine that are environmentally toxic. In this regard, Katti et al. have developed extensive work with phytochemical agents extracted from various biological media (e.g soybeans, tea leaves) [23][24][25]. It was demonstrated that these phytochemical agents performed the dual function of reducing the gold salt to form the AuNPs and at the same time provide a protein coating that can stabilize the nanoparticle structure [24][25].

As mentioned above, AuNPs can be obtained in various forms, including nanospheres, nanorods, nanoshells or nanocages. The synthetic methods described above are commonly used to obtain AuNPs in spherical amorphous form. The synthesis of AuNPs with a more complex shape requires alternative methodologies [18][26][27]. Gold nanorods (AuNRs) are commonly synthesized through the seed-mediated approach, which involves a two-step process where initially a seed solution is prepared with tetrachloroauric acid in the presence of a strong reducing

agent (e.g., $NaBH_4$) (Figure 3b). The seed solution is then added to a mixture of cetyltrimethylammonium bromide (CTAB), a mild reducing agent (e.g., ascorbic acid) and tetrachloroauric acid. The elongated ellipsoidal shape of the CTAB micelles permits the growth of the AuNPs of the seed solution in an elongated manner, in order to obtain a rod shape [28][29][30]. Some variations on this procedure include the addition of $AgNO_3$ prior to the growth phase, which allows a better control of the shape and increase the yield of AuNRs [28].

Besides the seed-mediated method, other methodologies have also been reported in literature for the synthesis of AuNRs. The template method is based on the electrochemical deposition of Au within nanoporous template membranes, which can be of different materials (e.g., polycarbonate or alumina). Ag or Cu is added to the template membrane to form a conductive film that allows for the electrodeposition of Au and growth of the nanoparticles within the membrane nanopores. The nanorods are then recovered by selective dissolution of the template membrane and Ag or Cu film. The diameter of the AuNRs is dependent of the nanopore diameter of the membrane, while the length can be controlled by the amount of Au deposited [31][32].

Electrochemical methods for AuNR synthesis are usually based on the use of a dual electrode electrochemical cell. A gold layer is used as the anode and a platinum layer as cathode. Both electrodes are immersed in a surfactant solution composed of the cationic surfactant CTAB and a more hydrophobic cationic surfactant like tetradodecylammonium bromide (TCAB), which are responsible for the formation of the rod-shaped nanoparticles. During the process of controlled current electrolysis, the gold layer releases Au ions that migrate to the cathode where reduction occurs and the AuNRs are formed [33].

Gold nanoshells (AuNSs) can be of two types, namely solid or with a hollow core (Figure 3c). The synthesis of core-containing AuNSs is based on the use of a seed nanoparticle, which will form the core of the nanoshell. Then, the addition of tetrachloroauric acid in the presence of a reducing agent leads to the deposition of gold seeds on the surface of the core. SiO_2 is one of the most commonly used cores. These silica nanoparticles have a capping agent on their surface, like 3-aminopropyltriethoxysilane (APTES), which provides NH_2 groups that can link to the gold [34].

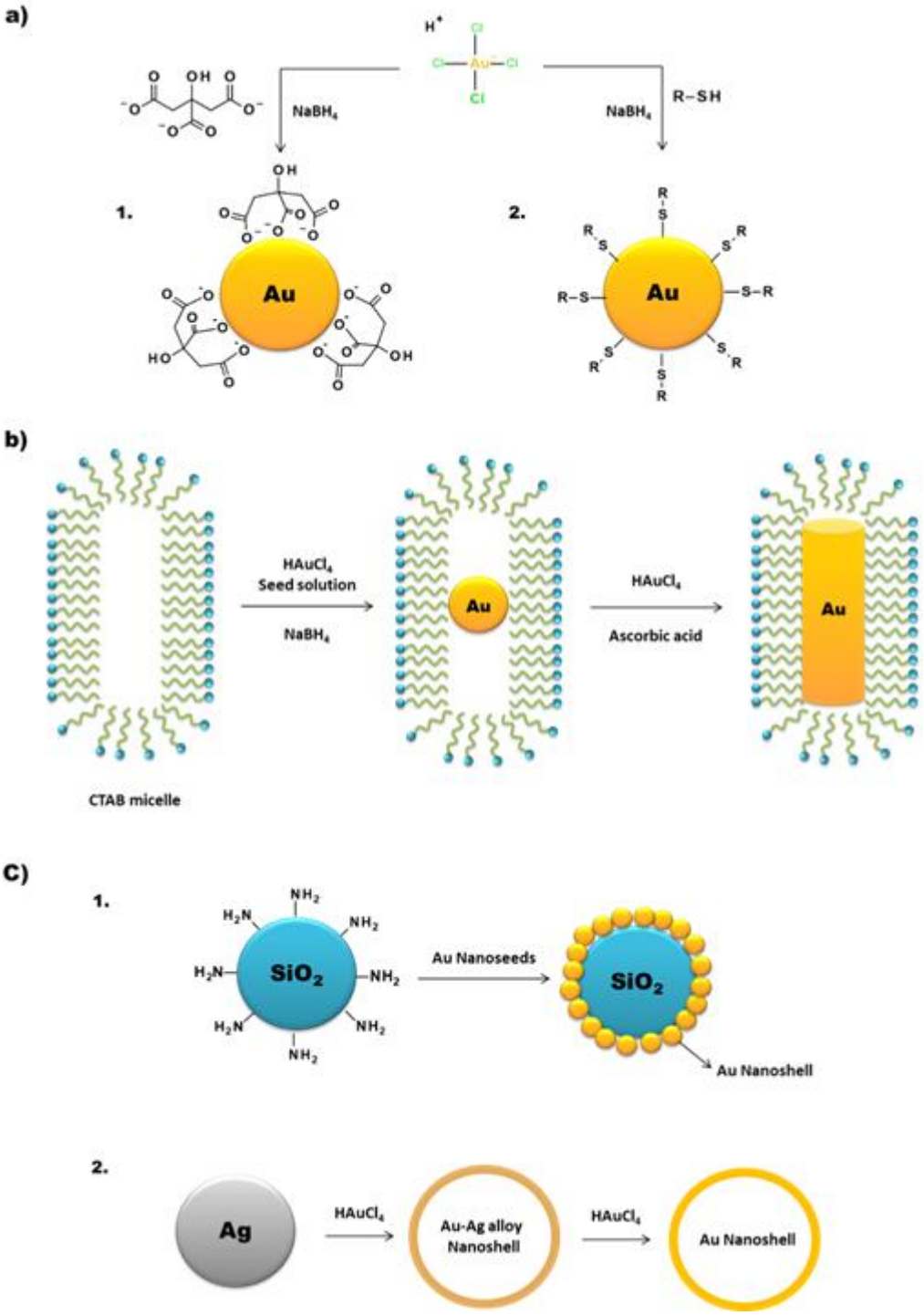

Figure 3. Schematic synthesis of (**a**) AuNPs by the 1) Turkevitch and 2) Brust methodologies, (**b**) AuNRs by the seed-mediated method, and (**c**) 1) core and 2) hollow AuNSs.

For the synthesis of hollow AuNSs, one approach is to use the silica core to synthesize the gold nanoshells as described above and then use HF to remove the SiO_2 core. Another method is the template galvanic replacement of silver. This methodology is based on the higher standard reduction potential of the $AuCl_4^-$/Au pair when compared with that of the Ag^+/Ag pair. Silver is oxidized into Ag^+ when silver nanostructures and $HAuCl_4$ are mixed in an aqueous medium. By optimizing the ratio between the silver nanoparticles and $HAuCl_4$, silver atoms can diffuse into the gold shell (or sheath) to form a seamless, hollow nanostructure with its wall made of Au-Ag alloys

[34][35]. The further increasing of the $HAuCl_4$ present in the medium triggers a dealloying process that selectively removes silver atoms from the alloyed wall. This induces morphological reconstruction that leads to the formation of pinholes in the walls, and the nanoparticles acquire a cage like structure. This is one of the common methodologies for the synthesis of gold nanocages (AuNCs). Temperature also plays an important role in the replacement reaction because the solubility constant of AgCl and the diffusion coefficients of Ag and Au atoms are both strongly dependent on this parameter [35].

Due to the inherent difficulties in analyzing nanoscale materials, in comparison with molecular or bulk materials, the characterization of NPs requires particular analytical techniques and methodologies. It is common to recur to various characterization techniques, in a complementary manner, to obtain reliable information on the NPs structure and their physico-chemical properties. Besides the techniques summarized below, there are various other methodologies available nowadays for NP characterization. The use of a single one of these characterization techniques cannot provide all the required data for a proper assessment of the NP structure, hence it is necessary to take into consideration the technique's strengths and weaknesses, depending on the nature of the NP [36][37].

Microscopy techniques, like transmission electron microscopy (TEM) or scanning electron microscopy (SEM), can provide information regarding the size and shape of the nanoparticles. On the other hand, the study of the hydrodynamic size distribution relies on techniques like dynamic light scattering (DLS) or nanoparticle tracking analyses (NTA), which can also provide information on the agglomeration state of the NPs in solution. Other commonly used techniques are zeta-potential measurements for surface charge determination and UV-Vis spectroscopy for characterization of optical properties, namely to determine the surface plasmon resonance wavelength that can be correlated with the size and shape of the nanoparticles. In the particular case of metallic NPs, X-ray-based techniques, like X-ray diffraction (XRD), are used to assess the crystalline structure and elemental composition [36][37].

3. Radiolabelling of Gold Nanoparticles

To pursue with a stable radiolabeling of AuNPs it is commonly required to perform their functionalization with suitable molecular entities, which will allow for the coordination/conjugation of the radioisotopes [38]. In this regard, there are different synthetic pathways available to functionalize AuNPs: (i) using bifunctional molecules that can act as a capping/stabilizing agent during the synthesis of the AuNPs and that can bind to the radioisotopes [39][40]; (ii) direct conjugation of amino/thiolated molecules to the surface of preformed AuNPs [41][42]; (iii) ligand exchange, in which some/all of the capping/stabilizing molecules on the AuNPs are exchanged with a different molecule with gold bonding capabilities [43]; and (iv) chemical modification of molecules already present in the AuNP structure [44][45].

Another way to incorporate radionuclides into the AuNP structure, without their further chemical functionalization, is by directly introducing the radioisotopes in the nanoparticle core (Figure 4). This is commonly achieved by using a $^{198/199}$Au precursor in the synthesis of the nanoparticles [46][47]. Alternatively, it has also been reported the neutron

irradiation of non-radioactive AuNPs to originate $^{198/199}$Au-containing nanoparticles through neutron capture reactions (^{197}Au(n,γ)^{198}Au and ^{198}Au(n,γ)^{199}Au) [48].

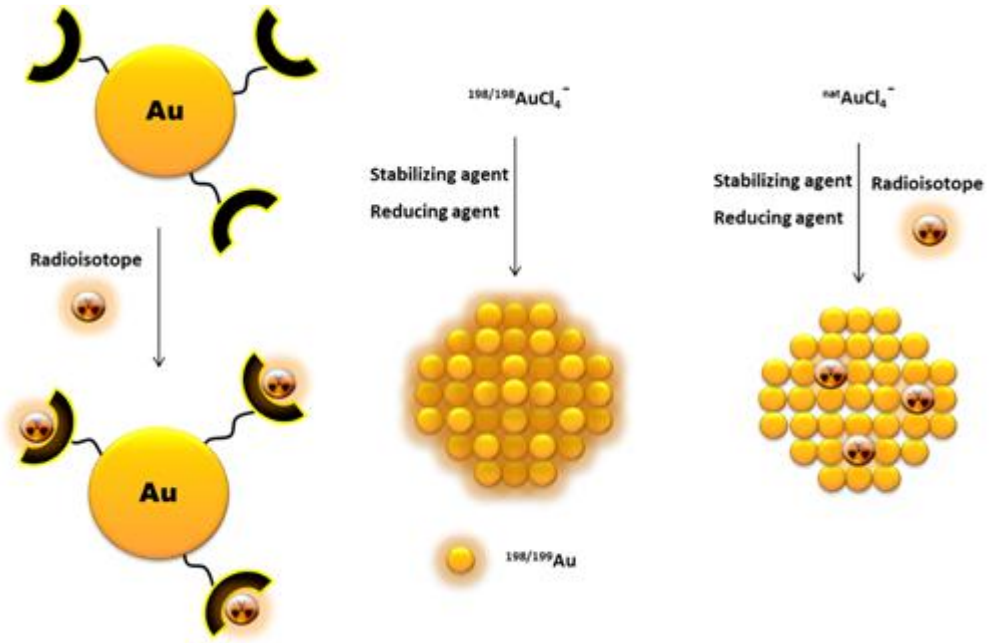

Figure 4. Schematic drawing of different pathways to incorporate radionuclides into AuNPs.

In some cases, it is possible to attach other radionuclides to the AuNPs without the need of extra chemical derivatization. This can be achieved by adsorption of the radionuclide to the AuNP surface, namely for ^{131}I or ^{64}Cu [49][50]. The incorporation of the radionuclide in the NPs core is another possibility, as reported by Liu et al. for ^{64}Cu alloyed AuNPs modified with PEG. These ^{64}Cu-labeled AuNPs were obtained starting from $HAuCl_4$ and $^{64}Cu(acac)_2$ and using oleylamine as reducing agent [51]. In the same way, Chen et al. have studied the integration of a ^{64}Cu shell into PEG-stabilized AuNPs by reducing ^{64}Cu(II) in the presence of hydrazine and polyacrylic acid [52].

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