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1. Supramolecular chemistry for Nanomedicine

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Abstract. Mimicking Nature, supramolecular chemistry represents the chemistry beyond the molecule, in view that intermolecular interactions constitute the driving force for the preparation of molecular and supramolecular assemblies, using the chemical information contained in molecular building blocks. Upon molecular recognition between discrete units, chemical processes such as self-assembly and self-organisation start operating, and are the leading processes to build up supramolecular aggregates and materials. When those materials have dimensions on the nanometric scale, a recently emerging scientific discipline is defined, Nanoscience. Nanomaterials are promising tools for many applications, and their use in biomedical and clinical applications defines the so-called Nanomedicine. In this review we present a few selected examples of nanomaterials designed for therapeutical purposes, emphasizing the importance of the preparation methodology in terms of their therapeutical use.

Introduction

Nanoscience frames the study, manipulation and control of chemical and/or biological materials at the nanoscale, which correspond to structures

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or systems with dimensions within the range of 1 to 100 nm ($1 \text{ nm} = 10^{-9} \text{ m}$) [1]. Within such nanoscale we could include supramolecular biological systems, such as cell membranes, nucleic acids or proteins, as well as supramolecular artificial nanostructured materials; amongst them, carbon nanotubes, liquid crystals, self-assembled monolayers or supramolecular systems based on colloids, like micelles or liposomes (Fig. 1). Nanoscience is a highly interdisciplinary field as the study of the properties of nanomaterials covers materials science, chemistry, physics and biology.

Two contrasting methodologies to create nanostructures are the so-called “top-down” and the “bottom up” approaches (Fig. 2). In the “top-down” approach, a block of material is taken and carved away until the object that is wanted is reached using techniques such as engraving, photolithography or milling. Thus, the top down approach is based in using nanoengineering and erosion to form the nanomaterial [2].

Instead, in the chemical approach (“bottom up”) [3], individual atoms and molecules are driven to or are placed precisely where they are needed by tools such as chemical synthesis, self-assembly or self-organisation. Therefore, supramolecular chemistry and the use of non-covalent interactions is the

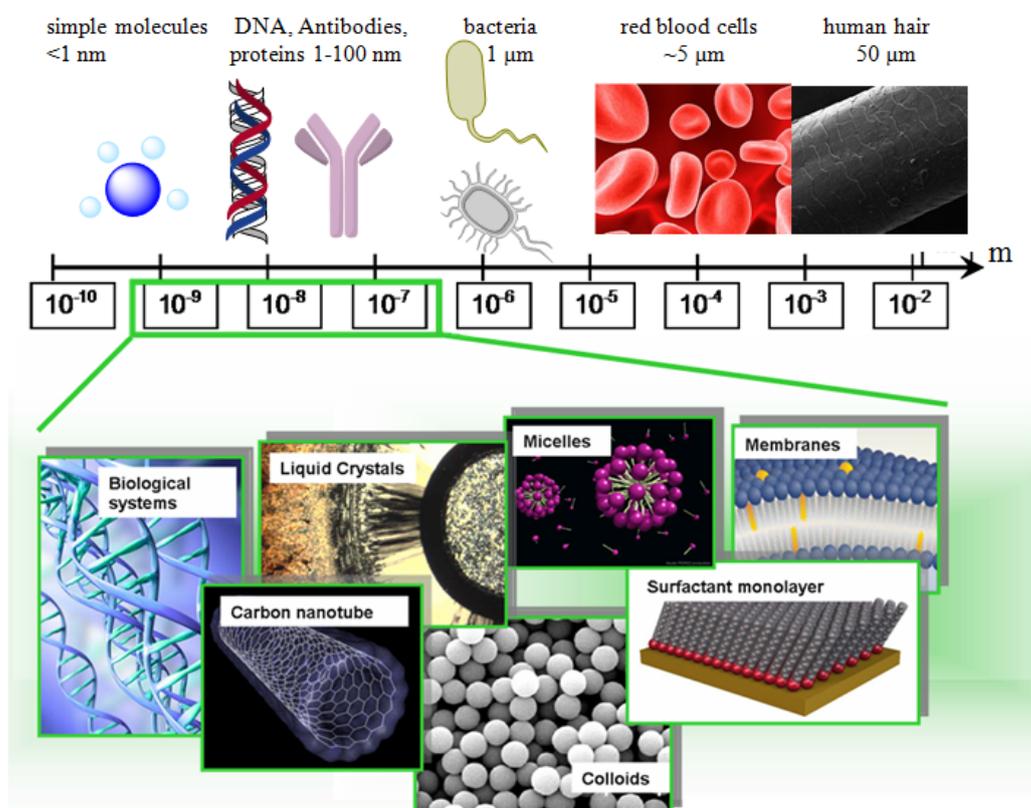


Figure 1. Size scale for different objects, including some soft materials within the nanoscale.

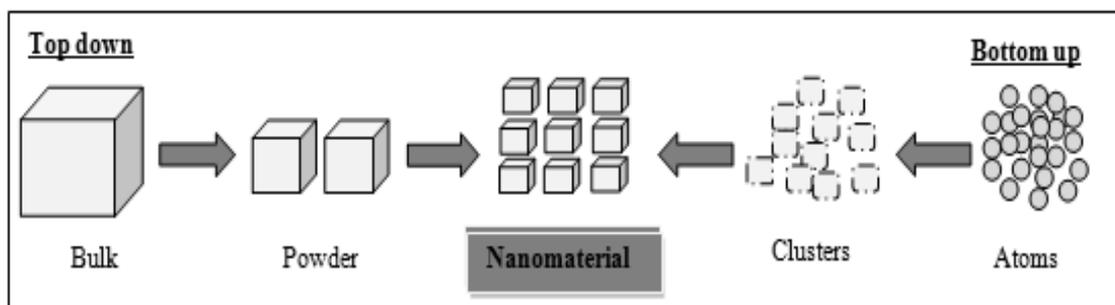


Figure 2. “Top-down” and “bottom up” approaches to the preparation of nanomaterials.

driving force to the formation of nanomaterials [4] by such approach, which relies mainly on the molecular recognition between the molecular components forming the supramolecular aggregates. Examples of this approach expand from the natural world (assembling nucleic acids or molecular motors) to the synthetic one to define the nanochemistry universe (Fig. 3).

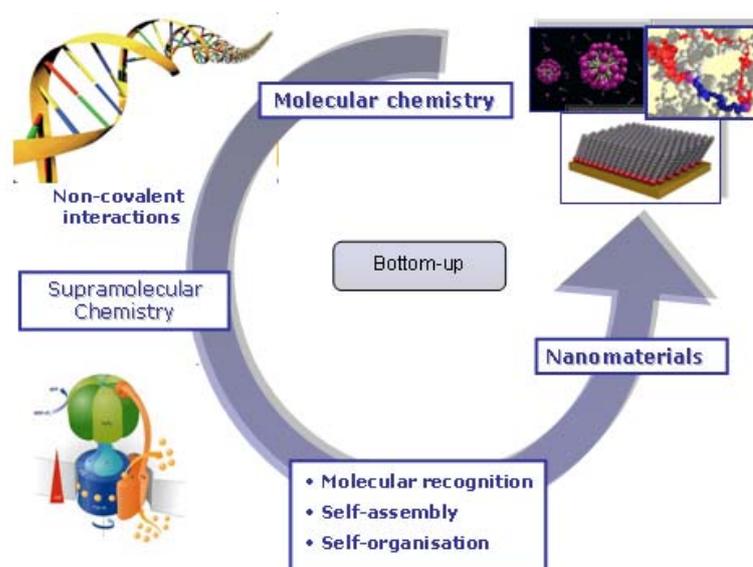


Figure 3. “Bottom up” approach and its driving forces.

On the crossroads between nanotechnology and medicine arises the field of nanomedicine, which is mainly understood as the use of nanotechnological concepts to target medical problems [5]. It is also agreed that nanomedicine revolves around three main areas: medical diagnosis –including imaging-, tissue regeneration and drug delivery (Fig. 4) [6]. In this sense, it could be differentiated from nanobiotechnology because this discipline is more centered on developing basic research to biological systems at the nanoscale [5].

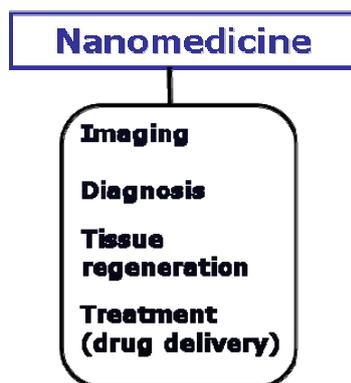


Figure 4. Applications of nanotechnology in medicine: Nanomedicine.

Beyond definitions, it is unarguable that both emerging fields are gaining much attention recently, and they rely on the use of nanostructured materials [7]. Thus, nanomaterials such as nanoparticles, nanofibers, nanowires and nanotubes have novel properties and functionalities which make them attractive to explore and modify biological processes, with potential applications in biomedicine [8]. Some of these nanomaterials are being envisaged and designed as multifunctional nanocarriers, aiming to perform functions as targeting, specific and selective delivering, and sensing [9]. Amongst them, nanoparticles used in drug delivery studies include liposomes, polymers, micelles, quantum dots, gold nanoparticles, paramagnetic nanoparticles and carbon nanotubes, although liposomes and micelles are so far the nanomaterials in clinical use (Fig. 5) [9,10].

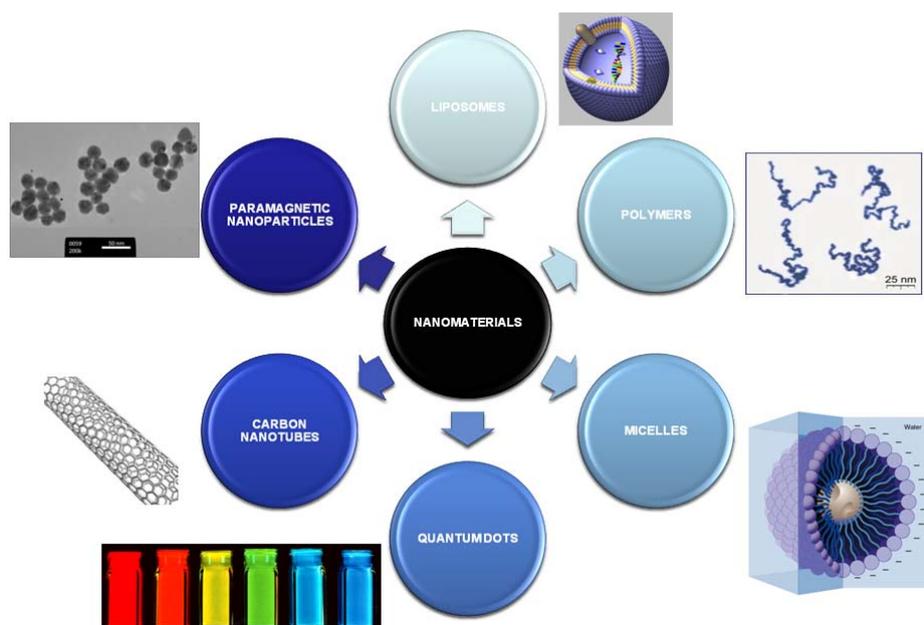


Figure 5. Nanomaterials for Nanomedicine.

In this review, and due to space limitations, a representative selection of examples was needed. Thus, considering the current research activity on this topic, and based in our own research experience, we have chosen some selected examples of the use of these nanomaterials, specifically gold nanoparticles, considered promising tools for both analytical purposes (diagnosis) and therapy (drug delivery). Additionally, we have included a section on self-assembled monolayers, as a representation of how powerful and relevant is surface chemistry for the preparation of functional nanomaterials and devices.

1. Gold nanoparticles in Nanomedicine

The benefits of gold have been known for centuries both in medicine and art (Fig. 6). Its use as medicine has been documented as far as 2500 BC, in China [11]. In the 17th century, one of the most popular ways of obtaining medicinal gold in solution was by dissolving elemental gold in *aqua regia* [12]. However it was not until Faraday's lecture, in 1857, that gold colloid was described as "diffused particles of gold", in a thorough study of its properties, where he described the relationship between the various processes used to obtain gold in different states (including colloidal gold), the sizes of particles obtained, and their relation with the light [13].

Recently, gold nanoparticles (GNPs) have been regarded with interest in the nanomedicine field as agents for labelling and imaging [14], diagnostic or carriers for delivery of biomolecules or small drugs, since they have many features that make them suitable for such applications. One that is of paramount importance is that the gold core is inert, and that GNPs, although



Figure 6. The Lycurgus Cup (British Museum, London) made of dichroic glass, contains colloidal gold and silver that gives its property of being translucent when a light is shone through it.

penetrating the cells, are mainly not cytotoxic. The degree of toxicity depends on the ligand that is stabilizing the gold core [15]. Also, is important the fact that they can be synthesized by simple methods that allow obtaining nanoparticles that are monodisperse, and the surface can be easily functionalized, mainly with thiols but also with others capping agents, such as amines [16], carboxylates [17], or phosphines [18]. There are many reviews focused on the applications of gold nanoparticles [19]. In the present review, we aim at giving a brief overview, with some recent examples found in scientific literature.

1.1. Preparation methods

The most widely used methods for the synthesis of the GNPs are the citrate method, developed by Turkevich, and the Brust-Schiffrin method. In the first one, the gold salt HAuCl_4 is reduced by citrate, which also has a stabilizing role [17]. Through this method, one can obtain GNPs that are water soluble, and varying the concentration of the reducing agent it is possible to tune the size of the particles. In the case of the Brust-Schiffrin method, the GNPs are obtained in a biphasic system [20]. In the organic phase there is a thiol, which acts as the capping agent that stabilizes and prevents the growth of the gold atom cluster. In the aqueous phase there is the reducing agent (sodium borohydride) and the gold salt HAuCl_4 . A phase transfer agent is needed, usually alkyl ammonium halides. The GNPs thus obtained are soluble in the organic phase. Since the surface of the GNP has a monolayer of the thiol attached, sometimes they are referred to as monolayer protected clusters (MPC). In literature, we can also find examples of GNPs that are stabilized by ionic liquids [21] and also gemini-type surfactants [22].

Based in the Brust-Schiffrin biphasic system, our group developed a novel method for obtaining GNPs, using a bis-imidazolium amphiphile of gemini-type synthesized in our laboratory [23] (Fig. 7). This method proved to be suitable for obtaining GNPs that are monodisperse, able to enter cells, with low toxicity, that furthermore could be loaded with a model drug, pursuing its delivery (see below).

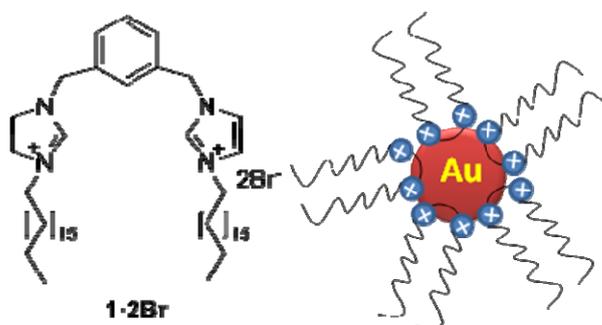


Figure 7. Bis-imidazolium amphiphile **1·2Br** (ref. [23]) and its distribution around the gold core of a gold nanoparticle.

1.2. Biomedical applications

GNPs suffer a phenomenon where the free electrons in the surface can absorb electromagnetic radiation, resulting in resonant oscillation. Due to this surface plasmon of the nanoparticles, i.e., propagating electron density waves occurring at the interface between metal and dielectric [14], they can be used as agents for labeling and imaging.

The Surface Plasmon Resonance (SPR) of the GNP can be used for diagnostic in Surface-enhanced Raman Scattering (SERS), which provides noninvasive *in vivo* imaging. The Plasmon resonance of the GNP increases the Raman effect of the molecules in the metal surface, with an increase in the signal by a factor of 10^{14} - 10^{15} . Gold nanoparticles were used successfully to detect early-stage inflammatory processes through SERS. They were conjugated with monoclonal antibodies specific for intercellular adhesion molecule-1 (ICAM-1) [24]. The ICAM-1 expression in endothelial cells can be linked to the progression of a wide range of inflammatory, autoimmune and infectious diseases. The GNPs were tested *in vitro* and *in vivo* and showed an S/N ratio that was over 2-fold greater than the one obtained with another technique based in fluorescence microscopy. This approach could also be used in the imaging of cancer cells expressing specific markers. For example, gold nanorods (GNR) were conjugated with a specific antibody and were used to target HER2, a biomarker overexpressed in MCF7 breast cancer cells [25]. Other example used GNP conjugated with antibodies specific for different cancer biomarkers, namely HER2 (overexpressed in breast cancer cells) and EGFR (overexpressed in various cancers). The GNPs showed great stability and good results *in vivo* [26]. The SERS could also be used to monitor the release in the nanomolar range of thiopurine anticancer drugs from the GNP surface (Fig. 8) [27].

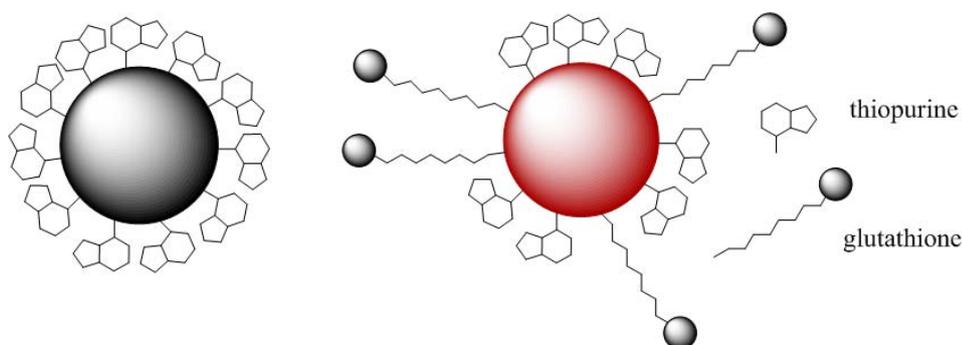


Figure 8. GNP with thiopurine on the surface. Inside the cells, the thiopurine is displaced from the surface by glutathione, it being released into solution, where its concentration can be monitored [27].

GNPs are also being used as contrast agents for Magnetic Resonance Imaging (MRI). In many cases, the nanoparticles have a magnetic core (for example, Fe_3O_4) and a shell of Au that allows further functionalization with the desired molecule on the surface. This type of nanoparticles was studied for the diagnosis and therapy of prostate cancer [28]. The nanoparticles were conjugated with a monoclonal antibody specific for the prostate stem cell antigen that prostate cancer cells overexpress. The monoclonal antibody (mAb) targets the cancer cells, but it is also used in immunotherapy. MRI was used to assess *in vivo* biodistribution of the nanoparticles-mAb conjugate. Manganese-gold nanoparticles are other example that is being studied. Mn^{2+} can be used as positive aqueous-based contrast agent for MRI imaging. These multifunctional Mn-GNPs were tested *in vitro* and *ex vivo*, and it was observed that they had low cell mortality and a high signal suitable for application *in vivo* [29]. Due to the versatility of these materials, alternatives are studied where the nanoparticles obtained can be used for both MRI and SERS [30]. In this case, the GNPs are complexed with iron oxide nanoparticles coated with dextran (Fig. 9). The dextran-iron oxide particles have already been studied as contrast agents for MRI, and the gold is deposited on its surface and functionalized with a reporter molecule that is used for detection through SERS.

Besides its use in imaging, GNPs can also be used as therapy agents, both alone, in photothermal therapy, or as drug delivery agents. In the first case, the photothermal therapy is based on the SPR of the GNP: when nanoparticles are irradiated with the adequate energy, they convert the light into heat that is responsible for the increase in the temperature, resulting in the ablation of the tumor [31]. Although the nanoparticles tend to accumulate in tumors (due to their high vascularization), the accumulation can be enhanced through the conjugation with ligands specific for the receptors that

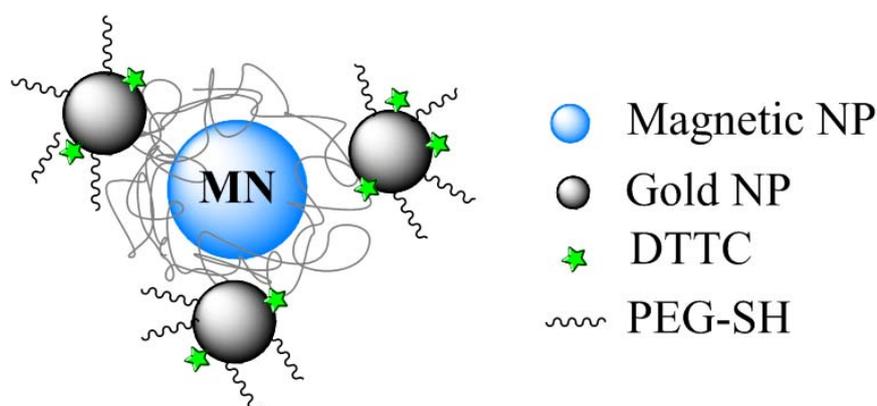


Figure 9. Iron oxide magnetic nanoparticles (MN) are covered with dextran. Gold nanoparticles (GNPs) are grown on its surface, and a thiol with PEG and a reporter molecule (DTTC) are attached [30].

are overexpressed on the tumor cells. One example found in literature is the use of ephrinA1-conjugated nanoshells. This ligand is specific for the EphA2 receptor that can be found in many prostate cancer cell lines. This approach was successfully used to target and destroy PC-3 prostate cancer cells *in vivo*, when a NIR laser was applied [32]. Similarly, colorectal tumors that overexpress guanylyl cyclase C (GCC) have been targeted through the conjugation of gold nanoshells with a heat-stable enterotoxin which is recognized by the receptor [33].

The work we developed in our group with imidazolium based gold nanoparticles included the study of their potential as a drug delivery system [23]. In this particular case, the synthesized gold nanoparticles (Fig. 10) were successfully used to incorporate an anionic model drug (ibuprofenate) and deliver it in a sustained manner. Furthermore, the nanoparticles presented relatively low toxicity, and could be internalized by cells.

GNPs are also widely studied to be used as drug vectors. For example, some amino-glycosidic antibiotics (streptomycin, neomycin, gentamycin and kanamycin) were conjugated with BSA capped GNPs, and presented *in vitro* better antibacterial activity than the antibiotics alone [34]. In a similar way, the conjugation of oxaliplatin to GNPs showed an enhancement in the delivery of the drug to lung cancer cell line A549 and colon cancer cell lines HCT116, HCT15, HT29 and RKO, besides an increase in the penetration in

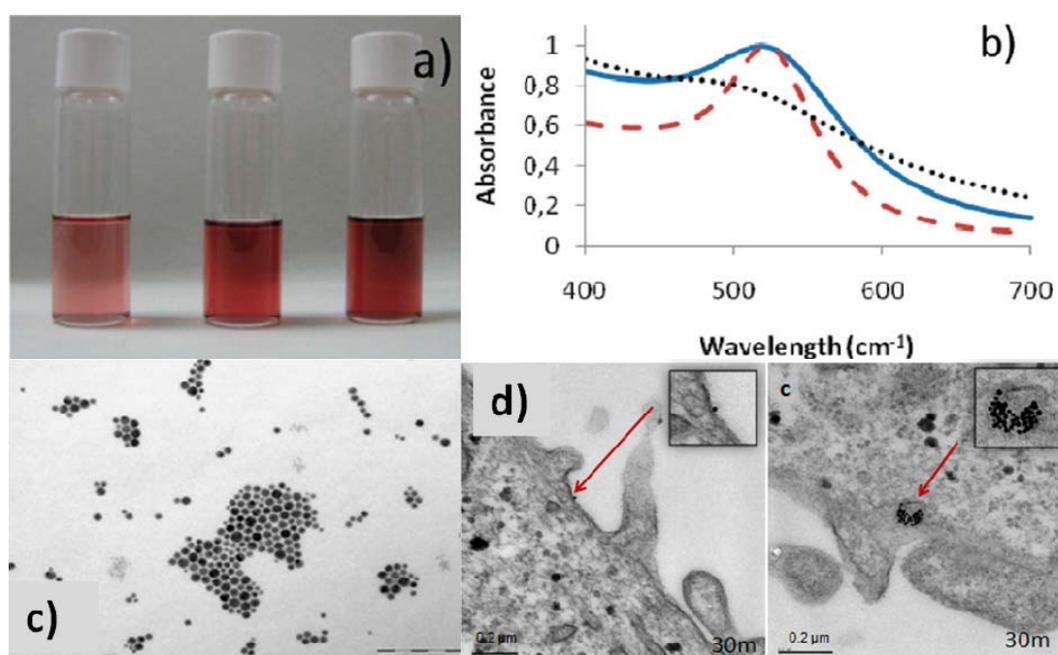


Figure 10. a) Images of gemini-imidazolium stabilized gold nanoparticles in dichloromethane, and images of their b) UV-Vis absorption spectra; c) TEM micrograph, and d) TEM images of nanoparticles internalized in Caco-2 cells [23].

the nucleus of the A549 cell line [35]. The enhancement can also be achieved through targeting, in the same way as described above for the GNPs used in imaging. For example, GNPs that were conjugated with curcumin, a potent anticancer molecule, and hyaluronic acid, which has strong affinity for cell surface markers CD44 and RHAMM. The markers are overexpressed in many types of tumors, probably because of the relation between hyaluronic acid and the angiogenesis. Furthermore, the GNPs were conjugated also with folate-PEG, to enhance their targeting ability, which resulted in the desired intracellular accumulation of GNPs [36]. The same folate ligand was used in GNPs conjugated with doxorubicin for targeting and delivery to tumor cells. Testing in A549 (non-expressing folate receptor) and KB (expressing folate receptor) cell lines showed a doxorubicin intake higher than for the drug alone in both cell lines, but the uptake was higher in KB cell line due to the folate receptor [37]. Similarly, GNPs synthesized with a copolymer of aspartate-doxorubicin and PEG, and conjugated with folate showed a drug release made in a sustained manner, depending on the pH of the medium [38]; the release is faster in acidic medium due to the hydrolysis of the hydrazone linkage. GNPs functionalized with a thiol-PEG derivative of tamoxifen, which competes with 17β -estradiol for the estrogen receptor alfa ($ER\alpha$), could be delivered selectively to breast cancer cells expressing ER, meaning that the receptor may aid the selectivity and uptake. The potency of the drug action in these breast cancer cells was up to 2.7 times higher [39]. GNPs covered with cyclodextrin, that provides a pocket to encapsulate β -lapachone, an anticancer drug, and functionalized also with anti-EGFR antibody, for targeting, were developed. In this case, the release of cyclodextrin from the GNP is induced by the presence of glutathione, followed by the release of the drug from the cyclodextrin pocket [40]. In this case, the GNP has a targeting function besides the triggered release of the payload.

1.3. Perspectives

Due to its versatility, GNPs are one of the nanostructured materials more widely studied, and has found application in distinct areas. Besides the given examples, the GNPs are also popular for use in diagnostic test kits. As outlined before, the examples shown here are just a small description. In the data below, one can see that the number of publications related with gold nanoparticles has seen an exponential increase (Fig. 11).

We expect to see very soon some of these systems clinically available, since they are being subject of active research in many fields, and show such promising results.

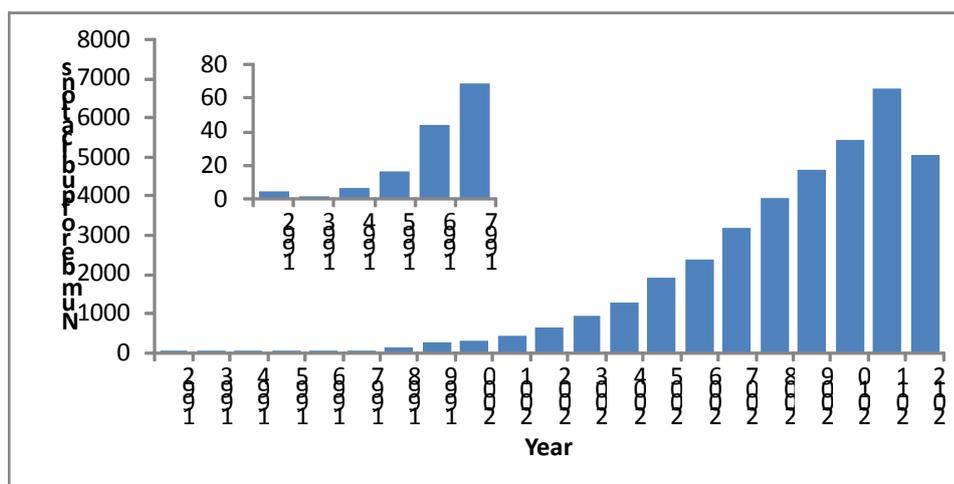


Figure 11. Number of publications with gold nanoparticles per year [41].

2. Self-assembled monolayers as (bio) sensors

Covalent immobilization of biomolecules or synthetic bioactive molecules onto solid supports is a key step in the area of biosensors, biotechnology and nanosciences [42]. One of the most currently used methods to immobilize biomolecules to substrates is the formation of an organic monolayer that will act as linker, the so-called self-assembled monolayer (SAM). SAMs are molecular assemblies formed spontaneously on metallic or inorganic surfaces by chemisorption between the substrate and a functional head group [43]. SAMs provide one simple route to functionalize surfaces by organic or biologic molecules containing free anchor groups such as thiols, disulfides, amines, silanes, or acids. The monolayer produced by self-assembly allows high flexibility with respect to several applications depending upon their terminal functionality or by varying the chain length (distance control). SAMs are also used as model substrates in biological studies because of their well-defined structure, controlled surface properties and biocompatibility. SAM formation allows the possibility of changing surface properties or to add new characteristics to the materials. The self-assembling molecules suitable to generate functional SAMs consist generally of three parts: the head group, the alkyl chain and the terminal end group (Fig. 12).

The head group is responsible for the anchoring of the molecules onto the substrate. The alkyl chain has a significant influence on the ordering of the SAM and provides the stability of the monolayer, due to van der Waals interactions. The terminal end group (functional group) introduces chemical functionality into the monolayer system and is important for the overall properties of surfaces because it allows the immobilization of the desired active molecule [44]. The control of chemical and physical properties of the

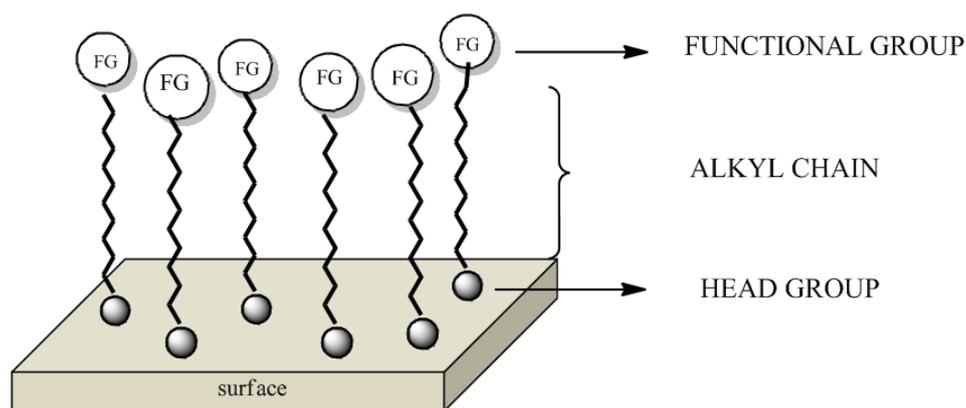


Figure 12. Fragments of functional SAMs.

SAMs has recently gained considerable attention, since, by selecting precursor molecules with adequate terminal functional groups, the functionalities of these surfaces can be regulated at the nanoscale.

2.1. SAMs formation and characterization

Different materials and assembling molecules have been employed as substrates for the formation of monolayers, but gold and silicon are the most widely used and studied because of the ease of using thiol and silane chains, respectively, to be attached onto the corresponding surfaces; they form well organized SAMs and they are biocompatible materials [45]. For example, SAM of long chain alkane thiol produces a highly packed and ordered surface, which can provide a membrane like microenvironment, useful for immobilizing biological molecules.

SAMs are formed spontaneously and can be produced usually through physical vapor deposition technique or by immersing a substrate into a solution of the molecule of interest (wet chemistry) [46]. SAM formation is a chemical process that depends on several parameters such as: deposition time, type of substrate and assembling molecule, type of solvent and deposition methodology. For example, to form a typical SAM on a gold surface, a diluted solution of the thiol in ethanol can be completed in less than 1 h, although the SAM will be more ordered if the deposition time increases. Fig. 13 shows a schematic representation of the thiol formation on a gold surface.

The best option to have a good characterization of a SAM relies on the combination of several analytical techniques, which is essential in order to confirm the SAM formation and ensure its functionality. One of the most used techniques is Atomic Force Microscopy (AFM), a very high-resolution

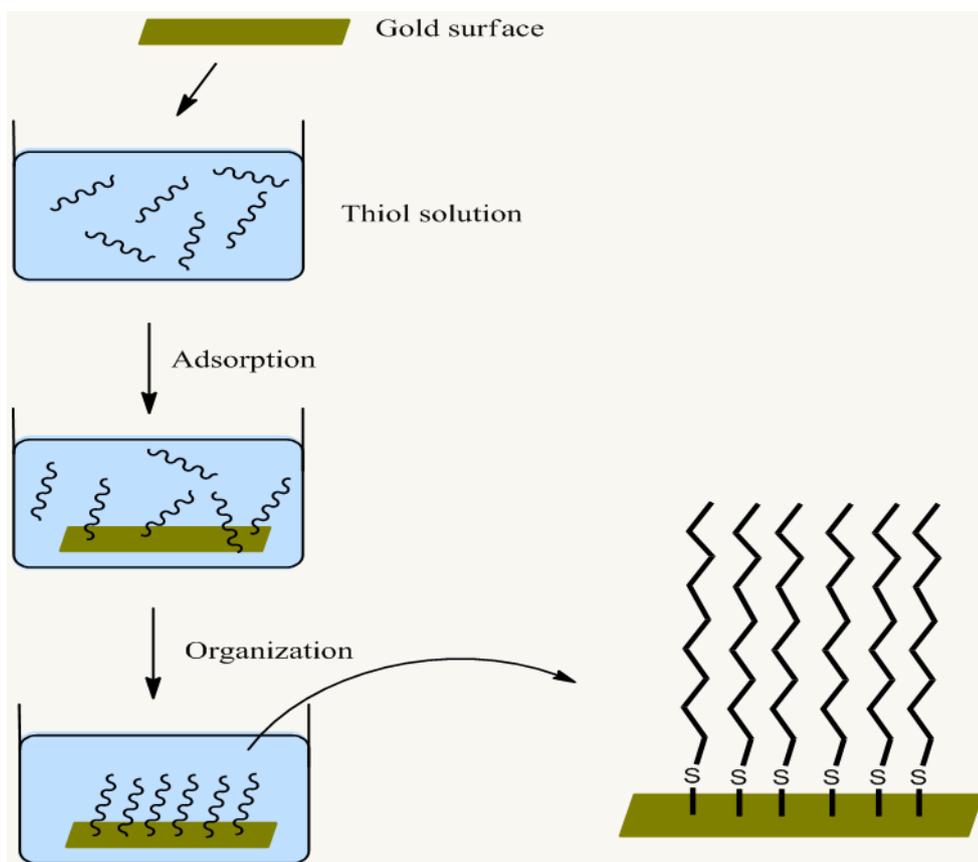


Figure 13. Schematic representation of SAM formation on gold.

type of scanning probe microscopy that allows the study of the surface coverage [47]. The information is obtained by "feeling" the surface with a piezoelectric (the cantilever), that explores the sample at the nanoscale with accurate and precise movements guided by a laser light from a solid state diode.

On the other hand, mass spectrometry techniques can be also used, such as matrix assisted laser desorption/ionization (MALDI-ToF MS), allowing the analysis of biomolecules and large organic molecules attached on the surface. MALDI MS has been used for SAM characterization first by Mrkisch, and it is used specially for gold surfaces because the fragmentation is lower and the total mass of the thiol can be detected [48]. Time of flight secondary ion mass spectrometry (ToF-SIMS MS) is a technique used to analyze the composition of solid surfaces, it being able to detect chemical elements or biological fragments such as amino acids [49]. Additionally, X-ray photoelectron spectroscopy (XPS) is a surface chemical analysis technique that allows the quantitative analysis of a material. XPS can measure the elemental composition, empirical formula and the chemical and electronic state of the elements present in a material [50].

Contact angle measurements are simple to make, and offer useful information about the hydrophobicity of a surface, and the changes that occur through surface modification. The method consists of depositing a drop of water on the functionalized surface and to record the angle formed between the drop and the surface [51]. Depending on the characteristics and the terminal group of the SAM, the hydrophobicity of the surface can be assessed. Fig. 14 shows an example of polysilicon functionalization methodology and the contact angle values associated to each chemical step. The initial polysilicon surface is quite hydrophobic ($\theta = 70^\circ$), but after hydroxylation the surface becomes highly hydrophilic ($\theta = 25^\circ$). Finally, when a SAM was formed using 11-triethoxysilaneundecanal (TESUD), the contact angle value increases noticeably, indicating the presence of the hydrophobic aldehyde SAM ($\theta = 98^\circ$) as well as a high level of surface functionalization.

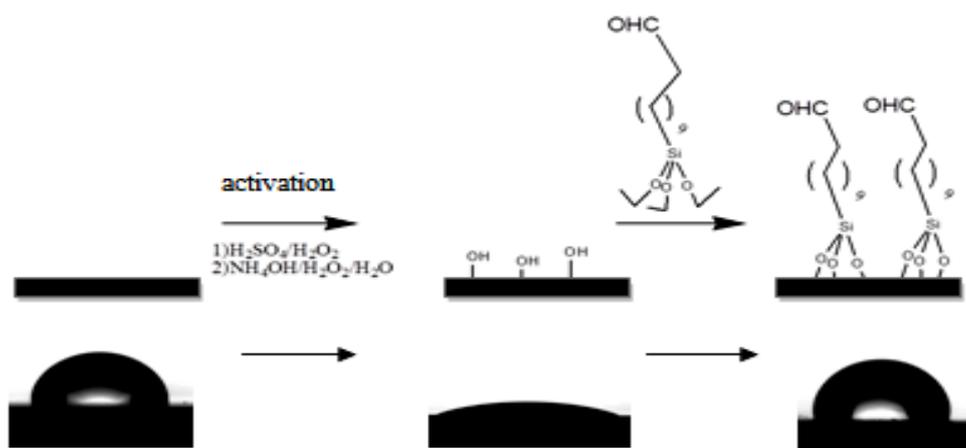


Figure 14. Contact angle measurements of clean polysilicon ($\theta = 70^\circ$), hydroxylated surface ($\theta = 25^\circ$) and TESUD monolayer ($\theta = 98^\circ$).

2.2. Biomedical applications of SAMs

SAMs have been studied and investigated in the last decade for their high range of applications in many areas such as nanotechnology, chemical surface sciences, biotechnology, chemical engineering or electronics. The activity and the utility of the SAM depend on the molecule that will be immobilized into the SAM using the reactivity between the functional group of the SAM and the desired molecule [52].

Biofunctionalization of SAMs with different biomolecules is of great interest to give biological properties to the substrate, and the preparation of biosensors is one of the main applications of the biofunctionalized SAMs

[53]. The selectivity offered by biomolecules such as antibodies, proteins, nucleic acids and enzymes or even organised systems like whole cells can be profitably used for molecular recognition. As a consequence, immobilization strategies for biomolecules are of paramount importance in order to preserve their biological activity. Various types of immobilization procedures are able to link the biomolecule with the substrate. These procedures could be classified according to the covalent and non-covalent natures of the linkage [54], although the covalent bond is more used due to their strength and stability.

Proteins and other biomolecules can be covalently linked to SAMs via the *N*-terminal amino group [55]. Primary amines react with activated esters by nucleophilic attack resulting in the formation of an amide bond. As it has been reported in the literature, two classical ester activating groups, the tetrafluorophenyl ester (PFP) [56] and the *N*-hydroxysuccinimide (NHS) [57] can react readily with amine containing biomolecules to obtain an amide bond (Fig. 15a). Also, the aldehyde group can be used to attach biomolecules covalently to gold or silicon surfaces [58]. In this case, the amine groups in the biomolecule react with the aldehyde groups in the SAM to generate a stable secondary amine linkage by reduction of the intermediate imine (Fig. 15b).

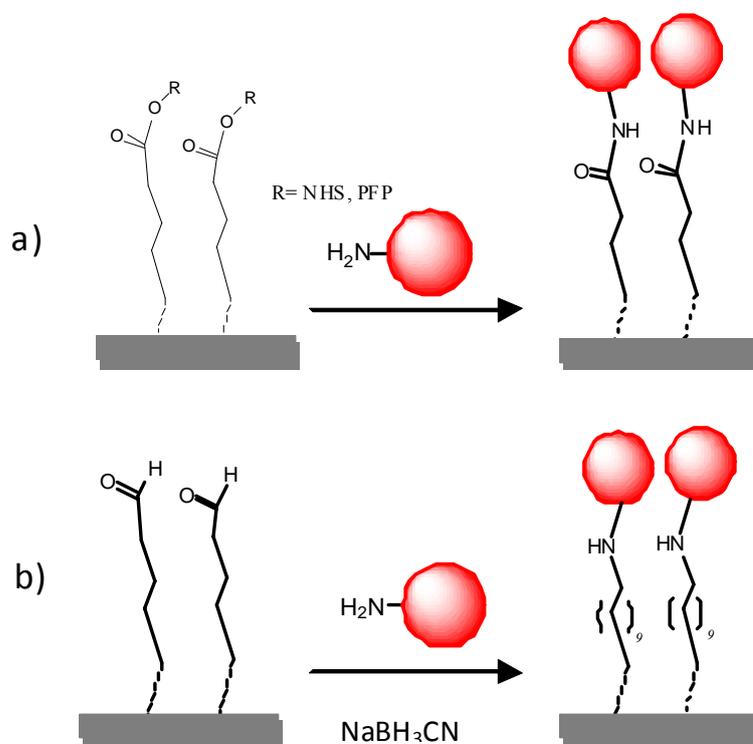


Figure 15. Protein immobilization through a) amide bond and b) amine linkage.

Examples of diagnosis systems based on SAMs are the personal glucose test devices or the pregnancy test kits [59]. Several biosensors also exist, of interest in Nanomedicine, based on the immobilization of antibodies or proteins that can recognize specific analytes. Fig. 16 shows an example of a protocol for the SAM formation on gold surface, followed by antibody immobilization and analyte testing for cancer detection [60]. First, a mixed SAM was structured using a) a terminal carboxylic acid thiol, which will react with the biomolecule, and b) a hydroxyl terminal thiol. The mixed thiols were chosen to provide appropriate organization and stability to the SAM, and to give the sufficient space to allow the active group to link the antibody. Next, a classical acid activation was done using NHS and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to connect the antibody covalently to the SAM. The immobilized antibody recognizes a specific antigen, thus acting as a nanobiosensor.

On the other hand, organic molecules can be also immobilized through a SAM. Normally, fluorescence moieties are included in the system, in order to detect changes depending on the parameter that has been studied [61]. The importance of sensing many biological processes has led to the development of fluorescence based organic receptors which can be used as chemosensors exhibiting a variation on their intrinsic fluorescence. The concept of organic receptor immobilization on functionalized substrates relies on detecting fluorescence changes in the presence of the given analyte (Fig. 17).

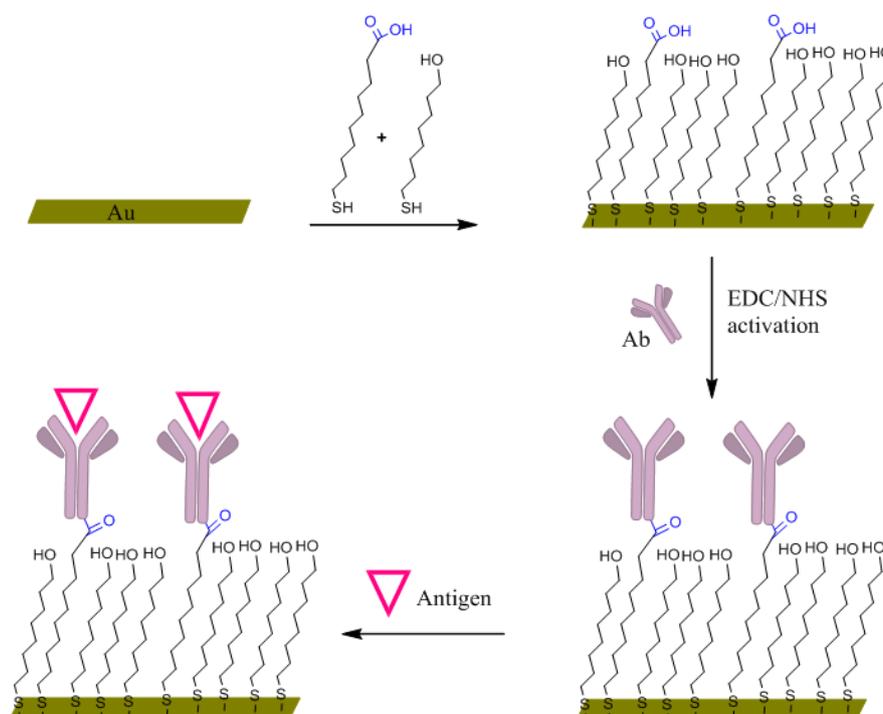


Figure 16. Antibody functionalization example.

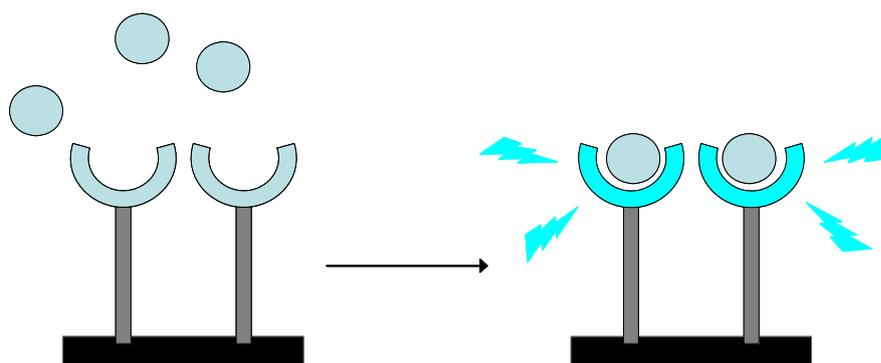


Figure 17. Model of fluorescence chemosensor.

Supramolecular chemosensors are composed of a binding part for guest recognition, and a sensing moiety to read information about the complexation.

Immobilized chemosensors have been studied in the last years for sensing important biological parameters at cellular level such as biological ions or radicals as well as enzyme activity, using fluorescence changes because it is one of the preferred methods for detection in living organisms [62]. As example of chemosensor, one of the biological parameters that has been studied in the last years is the level of various reactive oxygen species (ROS), because they are implicated in many intracellular processes going from apoptosis or cellular activity to a variety of inflammatory responses [63]. Fig. 18 shows a model of ROS sensor based on anthracene moieties [64].

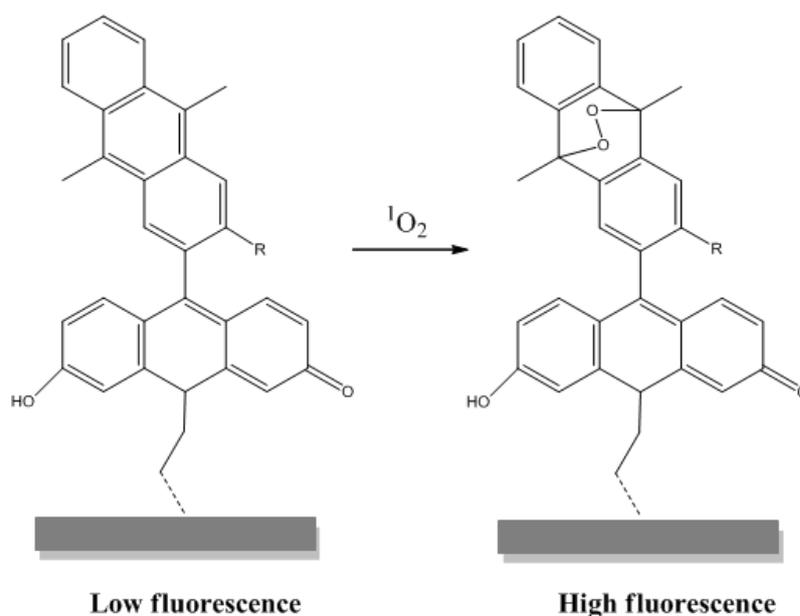


Figure 18. ROS formation induces change on the fluorescence emission of the immobilized anthracene containing derivative.

The presence of singlet oxygen detecting ($^1\text{O}_2$) produces the formation of an endoperoxide species, and the fluorescence of the complex increases. The system is hydrophilic, which is important for its use in biological samples, and furthermore, it is very selective for detecting $^1\text{O}_2$. Therefore, appropriated SAMs can be used as fluorescent probes for recognizing specific analytes in a selective manner, with potential usefulness as sensors for biological systems.

SAMs were also used recently by us pursuing cell tracking, a promising approach to individual living cells identification. Silicon barcodes were designed for extracellular tagging using photolithography processes [65] and were modified using chemical biofunctionalization. A self-assembled monolayer was used as a connector between the silicon material and the lectin wheat germ agglutinin (WGA) [66]. WGA was used because of its capacity to recognize some specific carbohydrates present on the surface of most mammalian cells. SAMs were prepared on polysilicon surfaces including aldehyde groups as terminal functions to study the suitability of their covalent chemical bonding to WGA. Fig. 19 shows an outline of the biofunctionalized barcodes that were tested doing adhesion experiments to the zona pellucida of mouse embryos. These experiments showed high barcode retention rates after 96 h of culture as well as high viability indicating the robustness of the biofunctionalization.

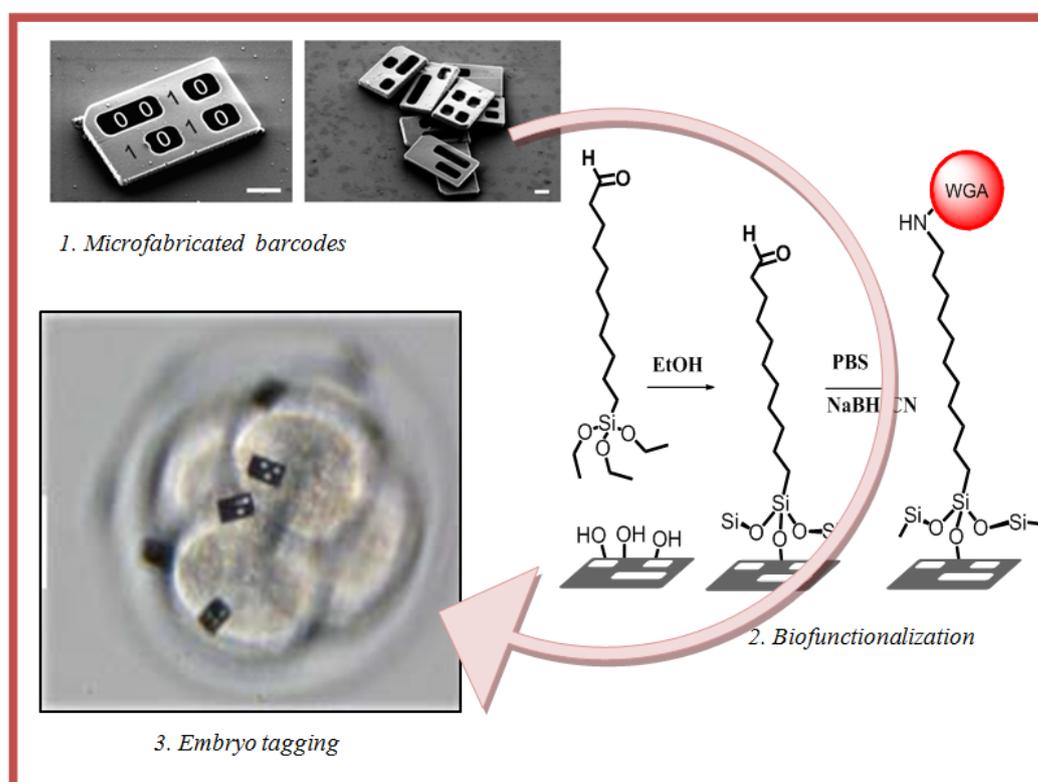


Figure 19. Representation of WGA biofunctionalized barcodes for embryo tagging.

3. Conclusion

We have shown various examples of nanomaterials of interest in Nanomedicine, mainly nanoparticles and self-assembled monolayers, some developed by our research group. The biofunctionality of any of the described nanomaterials is determined by a combination of an accurate design and selection of the components of the systems, as well as a shear control of the self-assembly processes governing their synthesis. Supramolecular chemistry lies behind any of these processes and it is central to any successful approach leading to new and promising nanomaterials for healthcare.

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