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Plasmonic Nanoparticles with Supramolecular Recognition

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Even after more than two decades of intense studies, the research on self-assembly processes involving supramolecular interactions between nanoparticles (NPs) are continuously expanding. Plasmonic NPs have attracted particular attention due to strong optical, electrical, biological, and catalytic effects they are accompanied with. Surface plasmon resonances characteristic of plasmonic NPs and their assemblies enable fine-tuning of these effects with unprecedented dynamic range. In turn, the uniquely high polarizability of plasmonic nanostructures and related optical effects exemplified by surface-enhanced Raman scattering and red–blue color changes gave rise to their application to biosensing. Since supramolecular interactions are ubiquitous in nature, scientists have found a spectrum of biomimetic properties of individual and assembled NPs that can be regulated by the layer of surface ligands coating all NPs. This paradigm has given rise to multiple studies from the design of molecular containers and enzyme-like catalysts to chiroplasmonic assemblies. Computational and theoretical advances in plasmonic effects for geometrically complex structures have made possible the nanoscale engineering of NPs, assemblies, and supramolecular complexes

with biomolecules. It is anticipated that further studies in this area will be expanded toward chiral catalysis, environmental monitoring, disease diagnosis, and therapy.

1. Introduction

1.1. Plasmonic nanoparticles

Plasmonic nanoparticles (NPs) can be defined as those particles with sizes between 1 and 100 nm, which can support localized surface plasmon resonances (LSPRs), i.e. collective electron oscillations in resonance with incoming light of specific wavelengths, thereby producing large electromagnetic fields near the nanoparticle surface.[1] The plasmon resonance effect results in strong enhancement of radiative properties of the NPs, such as scattering and absorption, and may even lead to the generation of energetic (hot) electrons that can largely influence chemical reactions.[2] For these reasons, plasmonic NPs have gained great momentum in multiple areas, such as electronics, catalysis, sensors, etc.[3]

Although several plasmonic metals exist, only a few can support plasmon resonances in the visible range of the electromagnetic spectrum, Ag and Au being the most frequent choices. Given the low stability of Ag NPs against oxidation, gold is the most widely used plasmonic material.[4] Additionally,

Au NPs feature other advantages beyond their plasmonic properties and high chemical stability; *e.g.* gold surfaces can be readily functionalized by taking advantage of the high affinity between gold and thiols. Surface functionalization enables high colloidal stability to the NPs while tuning their physicochemical properties.[5] Another important advantage is the comparatively low toxicity of metallic gold, which is even used as a food additive, owing to its chemical inertness and low tendency to be transformed into soluble salts under physiological conditions. These two properties have raised an enormous interest on Au NPs in medical and biological research, in some cases not even relying on their plasmonic behavior, but functioning as drug delivery units.[6]

An important characteristic of plasmonic NPs is that their optical properties can be readily tailored through control of their size and morphology.[7] Hence, the synthesis of Au NPs of different shapes has attracted increasing research interest during past decades. Nowadays, a wide range of NPs with high monodispersity in both geometry and dimensions can be synthesized using the chemistry of surface ligands.[8] The most common Au NP shapes comprise nanospheres, nanorods, nanostars (NSs), nanobipyramids, nanocubes and nanotriangles. Of particular importance are anisotropic Au NPs, i.e. nanorods (Au NRs) and nanobipyramids (Au NBPs), which feature narrow longitudinal LSPR bands that can be widely tuned by simply varying the aspect ratio of these NPs, from the visible into the near-IR spectral range.[9] One of the recently found properties is electrostatic anisotropy of NRs, which can be often hidden but has strong relevance in optics.[10]

A property of long-term interest for plasmonic NPs is the generation of high electromagnetic fields at their surface, which can be used to largely enhance the spectroscopic response of adsorbed or adjacent molecules, the most prominent example being Raman scattering spectroscopy. This effect is known as surface enhanced Raman scattering (SERS) and the corresponding enhancement factors can even reach 10^{10} – 10^{11}. Since its discovery in 1973, SERS has revolutionized the research field of

biological sensors, as even single molecule detection has been demonstrated using this technique.[11] In SERS applications, it is important to maximize the presence of regions where intense electromagnetic fields are concentrated, which are called hot spots. Hot spots can originate mainly from two different features: (a) sharp tips and edges in nanoparticles, or (b) hybridized plasmon modes resulting from coupling of the plasmon resonances of nanoparticles in close proximity; in this case the hot spots are localized at the gaps between NPs.[12] Importantly, the formation of hybridized plasmonic modes also typically induces a red-shift in the LSPR peak wavelength of the original NPs, which is useful toward developing colorimetric assays based on NPs aggregation.

It is worth noting that the application of anisotropic plasmonic NPs is partly limited by lower stability under certain conditions. For example, anisotropic plasmonic NPs can reshape at high temperature, which is mainly relevant to NPs with sharp tips, such as Au NBPs and Au NSs, with a tendency to become more rounded. For example, tip sharpness in Au NSs has been reported to get significantly reduced after only 30 seconds at 200 °C,[13] whereas transformation of Au NRs into spherical particles requires heating for 1 h at 250 °C.[14] An additional limitation that may hinder application in biological environments is the potential removal of coating ligands from the NP surface, due to exchange e.g. with natural thiolated molecules, a process that is accelerated under acidic conditions, or to oxidative desorption, thereby irreversibly altering their physicochemical properties.[15]

1.2. Supramolecular chemistry

Supramolecular chemistry is the discipline dealing with non-covalent interactions, i.e. with weak and reversible interactions such as electrostatic interactions, van der Waals forces, hydrogen bonds, metal–ligand bonds, and hydrophobic forces.[16] These weak forces are the reason why essential structures for life, e.g. DNA double helix and cellular membranes, can be formed. Furthermore, non-

covalent interactions are also responsible for the foundation of biological processes that are based on highly specific molecular recognition that is achieved through a strong synergy between weak interactions. Well-known examples of this kind of interactions are the recognition of specific DNA sequences by transcription factors[17] or enzymatic catalysis in which enzymes preferentially interact with transition states of chemical reactions, thus lowering the activation energy of a chemical transformation.[18]

Scientists have been trying to understand and emulate supramolecular complexes known from Nature. Over the last two decades, this effort has provided insights and spurring breakthroughs across chemistry, nanotechnology, biology, and materials science.[19,20] One of the main interests here has been the design of chemical entities capable of recognizing target molecules with high affinity and specificity. Towards this end, researchers have followed two different approaches, based on the type of host used to realize the recognition, either biomolecules or synthetic molecular containers.

Biomolecules, largely nucleic acids and proteins, have been extensively used to detect or capture guest molecules. If the target molecule is biologically relevant, in some cases it is possible to use a natural protein that has evolved for thousands of years, to achieve the recognition. Unfortunately, too often such a protein does not exist or it is difficult to be produced or isolated from the biological environment.[21] An alternative option is the use of antibodies (Ab), also known as immunoglobulins, which are large (150 KDa), Y-shaped proteins produced by plasma cells and essential to the immune system. Different Ab can bind to almost any target molecule, in a very specific way and with high affinity. For this reason, Ab have become essential reagents in many diagnostic applications.[22,23] Unfortunately, they are difficult to obtain; only eukaryotic cells can synthesize Ab because they need post-translational modifications, thus it is usually necessary to inject the target molecule or a

chemical entity that contains the target molecule into an animal to activate the immune systems so that the monoclonal Ab can be produced and isolated, therefore becoming expensive. Furthermore, like most proteins, Ab have low stability and need to be handled carefully to avoid degradation.[24] An additional alternative to antibodies are so-called "synthetic antibodies" or aptamers, which are normally nucleic acids that can also bind to a target molecule with high affinity and specificity, but with the advantage that aptamers are much smaller in size and can be synthesized chemically.[25]

Molecular containers are synthetic molecules that feature a cavity in which they can accommodate guest molecules.[26] They have been shown useful for multiple applications: detection of molecules, stabilization of high-energy reactive species, catalysis of chemical transformations, etc. The main advantages of such containers in comparison with biomolecules are their high stability and their straightforward preparation. An additional important advantage is that synthetic containers are not limited to the use of natural components for their preparation, and therefore they can bear non-natural functionalities in their structure to render appealing properties which are difficult to achieve with natural molecules.

1.3. Biomimetic properties of plasmonic nanoparticles

Supramolecular interactions give rise to the ability of NPs to self-assemble into complex structures. This line of logic can be further extended to consider the possibility of replicating some of the superstructures known from Nature by using NPs. The comparable size of NPs and biomolecules has accelerated the investigation in using plasmonic NPs as suitable building blocks for mimicking biological systems.[27] As shown in **Figure 1**, NPs can be engineered to display biomimetic structures and functions similar to those of biomolecules, by supramolecular chemistry. Surface modification with molecules or polymers leads to imitation of structures observed in nature, such as vesicles,[28]

cylinders,[29] and gels.[30] Like many types of organic molecules and biomolecules existing in living organisms, DNA and peptides can also endow chirality on NP assemblies and single NPs.[31,32] Apart from mimicking the architecture of many protein assemblies, for instance chains of the nanoscale units[33] or helices,[34] researchers have also investigated biomimetic functions by sophisticated fabrication of NPs, such as recognition and transport.[35,36] Additionally, either biomacromolecules (such as DNA, RNA and proteins) or small biomolecules (such as peptides or aptamers) can be bound to the NPs surface. Thus, utilizing the unique recognition ability of biomolecules, NPs can be assembled into designed spatial configurations. For applicability of NPs in nanomedicine and therapy, recognition plays a critical role related to specific binding with certain molecules, or pathogens. As the control over these functions gets more accurate, smart NPs approach clinical use for humans.

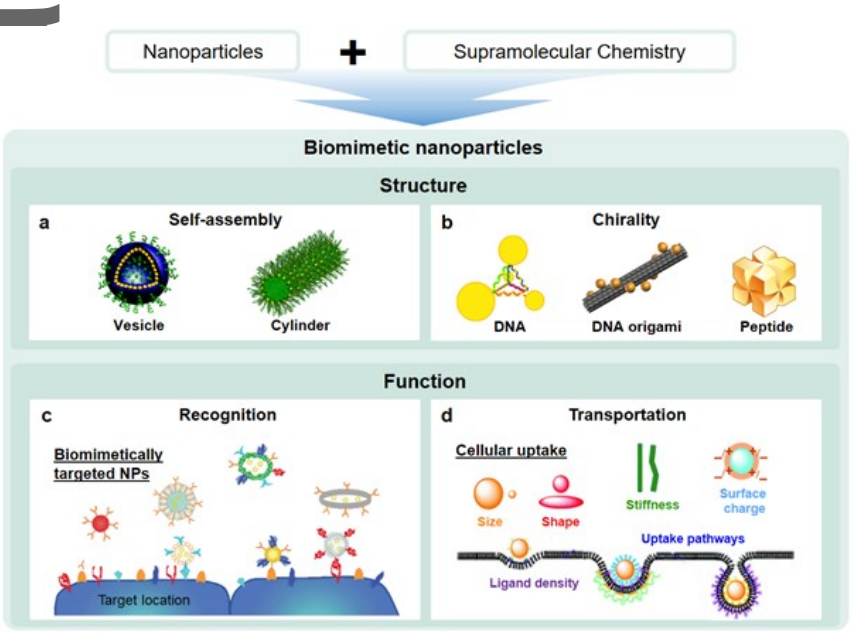

Figure 1. Biomimetic structures made of plasmonic NPs: a) self-assembled structure,[28,29] b) chiral structure.[31,32,37] Biomimetic function of smart NPs: c) recognition,[36] d) transportation.[35]

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We aim at presenting here how supramolecular recognition of and between plasmonic NPs can be utilized. We first highlight recent developments in the design of such materials based on molecular and nanoscale recognition. We then discuss optical, biological and catalytic effects emerging from the ability of NPs to form supramolecules. Chirality and chiroplasmonic properties representing a rapidly evolving area of research for plasmonic nanostructures are described in detail. Future opportunities and challenges are finally discussed, in terms of supramolecular NP assemblies and their biomimetic properties.

2. Plasmonic nanoparticles and molecular containers

This section is divided in four parts, based on the kind of molecular container used to endow plasmonic NPs with a specific "smart" behavior. In the first two sections, we discuss examples of the two families of containers that have been most commonly used in combination with plasmonic NPs, namely cucurbit[n]urils (CBs) and cyclodextrins (CDs). In the third section, we highlight the potential that more sophisticated and specific containers may have towards the design of functional NPs. Finally, the last section is dedicated to new approaches to obtain molecular containers based on plasmonic NPs.

2.1. Cucurbit[n]urils

Cucurbit[n]urils are a family of macrocycles synthesized via a condensation reaction between glycoluril and formaldehyde. They can act as a host for hydrophobic and/or small cationic molecules due to their unique ring-shaped geometry comprising carbonyl lined portals and a hydrophobic cavity. While CB[5], CB[6], and CB[7] usually accommodate only one guest molecule inside their cavity, the larger CB[8] can encapsulate more than one guest at a time to form ternary complexes. Owing to their simple hydrophobic cavity, CBs can interact with a wide variety of hydrophobic molecules, so that their specificity is much lower than for example aptamers. However, despite this limitation, they have been extensively used as supramolecular hosts due to their high stability and simple synthesis.[38]

CBs have attracted increasing research interest in nanotechnology because they can efficiently bind to Au NPs via their carbonyl portals,[39] thus they can be used as a chemical stimulus to induce the NPs aggregation. Importantly, several reports have shown that the interaction between CBs and Au NPs is dynamic and generates aggregates with highly rigid and fixed interparticle separations, with a constant value of 9.1 Å due to the CBs geometry. This is particularly interesting toward generating well-defined hot spots for SERS, which in general requires a uniform gap distance between NPs and the localization of analyte molecules precisely within such hot spots, so that a highly reproducible SERS signal is obtained. Interestingly, CBs are Raman-active molecules themselves, and can therefore be used as SERS reporters forming self-calibrated *in situ* SERS substrates, to determine the near-field strength at the nanojunctions.

In addition to advantages arising from the use of CB as a connector for NPs, the role of CBs as hosts can be harnessed in sensing applications to place a target analyte in the very center of the hot spot. This approach has been applied to the detection of inert molecules that cannot be detected by SERS due to their low affinity for the metallic surface of plasmonic NPs. For instance, as a proof of

concept, the molecule ferrocene was sensed using CB[7], for which a SERS enhancement factor of 10^9 was obtained.[40] A similar approach was subsequently applied to detect more relevant analytes such as polyaromatic hydrocarbons (PAHs), which are a class of pollutants that must be monitored at ultralow concentrations, but their low affinity for SERS substrates hinders ultrasensitive detection. In this work, a high affinity between CBs and PAHs was achieved by means of an elegant strategy where a ternary host-guest complex was formed between the host CB[8], a fixed electron deficient first guest and the PAH analytes as a second guest (**Figure 2a**-**b**). Thus, the formation of the ternary complexes was stabilized in water through hydrophobic forces, as well as π−π interactions between the two guests, thereby enabling the identification of five different PAHs with detection limits as low as 10^{-11} M.[41]

The application of CBs for SERS detection has received considerable attention, to the point that this powerful strategy was shown to achieve single-molecule SERS detection.[42] On the other hand, the concept of a SERS-nanoreactor has also been demonstrated, in which CB sequesters reactants into its internal cavity and their optimal location within the hot spot enables chemical reactions in the cavity to be monitored, both in situ and in real-time. This has been proved using diaminostilbene, as this molecule forms a 2:1 inclusion complex with CB[8] and upon photoirradiation results in [2 + 2] photodimerization of diaminostilbene, with high yield.[43] Additionally, when CB[7] is used instead of CB[8], forming only a 1:1 complex with diaminostilbene, it is possible to follow by SERS the trans → cis isomerization of this molecule upon irradiation (**Figure 2c**-**d**).

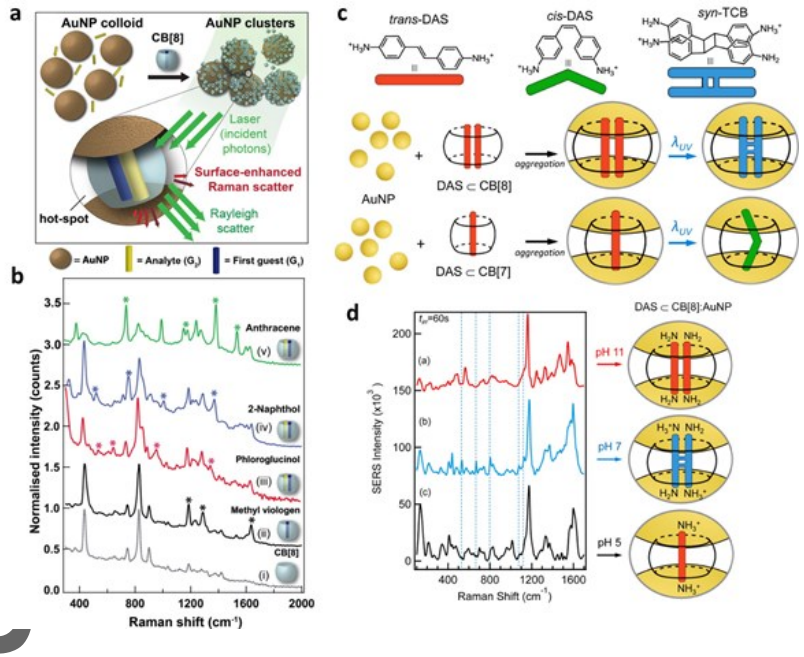

Figure 2. a) Schematic representation of Au PNs aggregation induced by CB[8], which enables SERS detection of polyaromatic hydrocarbons through the formation of a ternary supramolecular complex. b) SERS spectra of CB[8] in i) the absence and ii–v) in the presence of different PAHs and a fixed electron-deficient guest (5 µM). Reproduced with permission.[41] Copyright 2012, American Chemical Society. c) Schematic of diaminostilbene (DAS) photodimerization and photoisomerization in the presence of CB[8] and CB[7], respectively. d) SERS spectra of DAS and the photodimerization product when encapsulated in CB[8] between NPs. Reproduced with permission.[43] Copyright 2013, American Chemical Society.

Although the main use of CBs in combination of plasmonic NPs has been SERS detection, their applications are not limited to molecular sensing. In 2010, Rotello's group proved for the first time, that the host-guest properties of CBs can be applied to control the biological properties of metallic NPs. In this groundbreaking work, a supramolecular system was devised to control the toxicity of diaminohexane-terminated gold nanoparticles (2 nm diameter). When the diaminohexane ligand

forms a host-guest complex with CB[7], the NPs become non-toxic and in addition they are readily taken up by cells, where they remained trapped within endosomes. Addition of the guest molecule 1-adamantylamine, featuring a very high affinity to CB[7], causes the intracellular disassembly of the complex. Notably, the removal of CB from the surface of NPs activates their cytotoxicity, which first leads to endosomal escape of the NPs and subsequently the NPs induce cell death.[44]

A second biological application of CBs in combination Au NPs was reported in 2015 by the same research group, using a similar system. In this case, the authors showed that the host-guest complex formed between CB[7] and a ligand covering the NP surface can be used as a gate-keeper system (**Figure 3**). Towards this end, Au NPs capable of encapsulating hydrophobic transition metal catalysts, such as [Cp*Ru(cod)Cl] (Cp*=pentamethylcyclopentadienyl, cod=1,5-cyclooctadiene), were designed. Upon encapsulation of the metallic complex, the water-soluble NPs can act as catalysts, but the addition of CB[7] can be used to block the access of molecules to the catalytic site, resulting in essentially complete inhibition of the catalytic activity (**Figure 3b**). The gatekeeper molecule, CB[7], can be released from the surface of Au NPs using competitive guests, so that the catalytic activity is restored (**Figure 3c**). This reversible system has been applied inside living cells to trigger the cleavage of allylcarbamates for pro-fluorophore activation and propargyl groups for prodrug activation.[45]

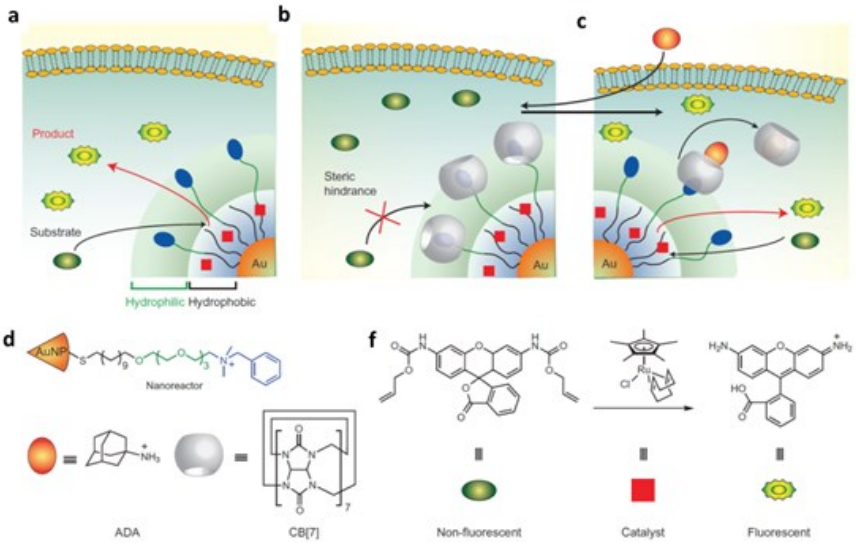

Figure 3. Schematic representation of a gate-keeper system based on Au NPs and CB[7] to accomplish intracellular catalysis. a) The Au NPs with the metal catalysts encapsulated perform intracellular catalysis. b) After CB[7] complexation the catalyst is inhibited. c) The activity is restored through addition of the competitive guest 1-adamantylamine (ADA). d) Structures of the NP platform. e) Catalytic pro-fluorophore activation performed inside the cell by catalyst embedded catalyst in the Au NPs. Reproduced with permission.[45] Copyright 2015, Nature Publishing Group.

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As shown above, the supramolecular recognition of CBs can be used to reversibly change certain properties of NPs, even in biological environments. Unfortunately, in order to achieve this level of control, chemical stimuli need be used. Such strategies are however difficult to apply in living organisms. Conversely, physical stimuli such as near-IR light, magnetic fields, or ultrasound, are ideal triggers for biological applications since they are harmless to biological tissue.[46] Recently, an

approach has been reported toward the release of guests from CBs using near infrared light. Gold nanostars decorated with CB[7]s were able to encapsulate the dye 6-aminocoumarin (6-AC), which forms a stable 1:1 host-guest complex with CB[7]. Interestingly, the binding strength of the guest and CB[7] dramatically decreased with the increase of temperature. Thus, when nanostars were irradiated with near-IR light, the temperature of the solution increased due to the photothermal conversion properties of Au NPs, in turn leading to release of the cargo. However, it is worth noting that this strategy has not been applied in the presence of cells.[47]

2.2. Cyclodextrins

Cyclodextrins are a family of cyclic oligosaccharides, composed of α-(1,4) linked glucopyranose subunits. They are synthesized as a result of an intramolecular transglycosylation reaction from the degradation of starch by the enzyme cyclodextrin glucanotransferase.[48] Due to the chair conformation of the glucopyranose units that form CDs, they have a torus-like shape with a hydrophilic outer surface and a lipophilic cavity. Therefore, CDs can readily host hydrophobic molecules in their cavity, while their exterior is sufficiently hydrophilic to endow aqueous solubility to the host-guest complex. The most common cyclodextrins are α, β, and γ, consisting of 6, 7, and 8 glucopyranose units.[49] In contrast to CBs, CD functionalization can be readily performed, therefore, it is possible to manipulate their host–guest behavior or covalently attach all types of molecules to them. One example of modification of CDs toward binding onto metal NPs, is the replacement of one of the primary alcohol groups of the CD for a thiol moiety, which can be achieved in only two steps.

Although CDs can bind a variety of hydrophobic molecules, photoresponsive molecules such as azobencenes and spiropyrans are the most frequently used guests. Azobenzenes undergo reversible

trans-to-cis isomerization upon irradiation with UV light, and the reverse cis-to-trans using visible light or heating. The trans-azobenzene forms a strong 1:1 host-guest complex with both of α and β-CD in aqueous environment, whereas the cis isomer does not fit in the hydrophobic cavity of CDs, and therefore it triggers dissociation of the complex when formed.[50] This strategy has been extensively used to design photoresponsive supramolecular systems.

Azobenzene/cyclodextrin host-guest complexes were also applied to plasmonic NPs. In an early piece of work, a photoresponsive system was developed to control the linear assembly of Au NRs in a reversible manner, by using NRs decorated with thiolated β -CDs only at the tips and a soluble guest that carries azobenzene on both ends. The guest, which could therefore interact with two CD at the same time, was used as a chemical stimulus to induce the alignment of Au NRs. As expected, the alignment could be disturbed upon irradiation with UV light (365 nm), due to the conformational switch into cis-azobenzene.[51]

The azobenzene/cyclodextrin host-guest complex was subsequently used to develop a supramolecular strategy for the reversible phase transfer of Au NPs between water and toluene, induced by irradiation with UV and visible light (**Figure 4a**-**b**).[52] Such a supramolecular system comprised azobenzene-containing surfactants and Au NPs (4 nm diameter) fully covered with thiolated α-CDs. In the initial state, α-CD-coated AuNPs were dispersed in the aqueous phase, due to the hydrophilic nature of the outer surface of CDs, while the trans-azo-ligands were dissolved in toluene. Once the biphasic system was gently stirred, the trans-azo-ligands could bind to the α-CDs on the Au NP surface, in turn bringing the hydrophobic alkyl chains of the azobenzene derivative onto the Au NP surface. Thus, the Au NPs switched from hydrophilic to hydrophobic and were transferred into the toluene phase. Subsequently, the initial hydrophilic Au NPs could be recovered using UV irradiation, which isomerized the azo-ligand from the trans into the cis state. This cis-azo-ligand did not fit in the CD cavity and therefore left the AuNP surface, thereby inducing the phase

transfer of Au NPs, back into water. Finally, the water-to-toluene phase transfer process could be repeated when the cis-azo-ligands were converted into the trans state by irradiation with visible light. This process could be repeated for multiple cycles by simply alternating UV/vis irradiations and was used to control catalytic reactions. For example, Au NPs capped with α-CD are known to catalyze the reduction of 4-nitrophenol to 4-aminophenol, in the presence of sodium borohydride, only in aqueous solution. When Au NPs were transferred into the toluene phase the catalytic reaction was quenched, but after irradiation with UV light the Au NPs could return to the aqueous phase and catalysis was recovered.

Although the azobenzene /cyclodextrin strategy has been extensively applied to develop light-responsive systems, azobenzenes have two important drawbacks: the thermodynamic stability of the cis isomer is usually low, and the overlapping absorbance of both (cis and trans) isomers leads to incomplete photoswitching. More recently, water-soluble arylazopyrazoles were reported, which could be used in CD-based supramolecular systems, featuring superior photoswitching properties compared to the standard azobenzenes. Additionally, these new systems were also successfully applied to control the reversible aggregation of Au NPs.[53]

2.3. Tailor-made containers

Despite the large number of potential applications that have been demonstrated for cyclodextrins, cucurbiturils, and similar capsules, they also feature significant drawbacks. The main limitations are related to their simple (lack of functional groups toward the interior), open, small and hydrophobic cavity, which provides these containers with relatively low specificity, and allows them to interact with small hydrophilic molecules only. Toward fixing this limitation, the design of more elaborated

hosts has attracted the attention of researchers in the supramolecular field.[54,55]

In the 1990s, an appealing way of preparing molecular containers was reported, based on the self-assembly of small, complementarily-functionalized building blocks. Such a methodology not only facilitated the synthesis of molecular containers, but also triggered the discovery of a large number of containers with designed functionality. One important aspect of the self-assembly strategy is its error-checking character, meaning that the container must be the thermodynamic product of a reversible process that can be based on metal/ligand interactions, hydrogen bonding or hydrophobic forces.[56] Unfortunately, although such containers did show appealing host-guest properties, including high specificity, encapsulation of biological molecules and catalytic properties, their low stability in the presence of coordination groups such as amines, thiols and carboxylic acids have largely hampered their application.[57] Recently developed strategies make use of a post-assembly modification to stabilize these supramolecular assemblies. This is e.g. the case for the use of metal–organic containers as precursors to prepare fully covalent containers, by means of borohydride reduction.[58] By using this strategy a water-soluble covalent container with high affinity and specificity for the dye pyranine was obtained.[59]

Due to the almost unlimited number of complex molecular containers that can be readily prepared using the self-assembly process, we envision that such containers will likely revolutionize the design of plasmonic nanostructures. One early example of their potential was the development of a supramolecular strategy for the spatio/temporal control of the uptake of small Au NPs by cells, based on the above mentioned pyranine-specific covalent container (**Figure 4c**-**d**). This approach relied on the modulation of Au NPs surface charge via decoration with negatively charged pyranines, which hampered the NP cell internalization, owing to the build-up of a high negative surface potential that repels cell membranes.[60] However, NP internalization could be efficiently activated upon addition of the covalent container, which is positively charged and interacts with pyranine

forming a positively charged host-guest complex on the NPs surface. The methodology is compatible with complex biological media due to the high specificity of the container for pyranine molecules. Furthermore, the system is susceptible to on/off regulation by rational addition of either container or free pyranine, which competes for the cage with the pyranine bound to the NP.[61]

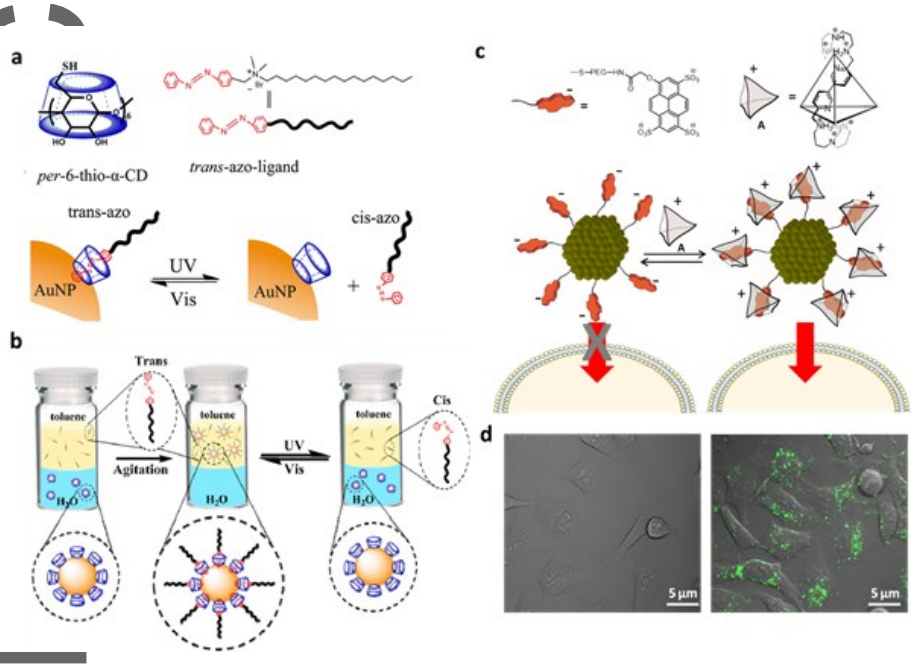

Figure 4. a) Structures of host thiolated α-CDs (per-6-thio-α-CD) and the guest azobenzene-containing ligand (azo-ligand). b) Photoreversible inclusion of azo-ligand in the NPs coated with the thiolated α-CD. c) Light-responsive phase transfer of α-CD-capped Au NPs by azo-ligands between the water and toluene phases. Reproduced with permission.[52] Copyright 2014, Copyright 2016, American Chemical Society. c) Schematic representation of the approach to control the cell internalization of Au NPs by formation of a supramolecular host–guest complex between the pyranine moiety and the positively charged covalent container **A**. PEG = poly(ethylene glycol). d) Fluorescence microscopy images of HeLa cells incubated for 1h in PBS after two washing steps in the

absence of **A** (top) and in the presence of 5 μM of **A** (bottom). Reproduced with permission.[61] Copyright 2018, American Chemical Society.

2.4. Synthetic containers based on nanoparticles

We have discussed so far the way molecular containers can be applied, in combination with NPs, to design supramolecular systems. In this section we discuss a different strategy, in which Au NPs are the building units to obtain supramolecular containers. The synthesis of these synthetic containers is very simple, as they are formed when Au NPs aggregate, leading to the formation of void spaces between the ligand shells of the gold-core building blocks. Importantly, the size of the void spaces can be controlled through the size of Au NPs, while the polarity is determined by the type of ligands covering the Au NP surface. It should be noted however that, despite their straightforward preparation, these cavities have received little attention because their use is limited due to the slow diffusion of molecules in their interior.

A groundbreaking work by Klajn's group demonstrated for the first time the potential of these cavities, overcoming the diffusion limitation by creating and destroying NP aggregates in a reversible fashion, using light at two different wavelengths.[62] To achieve such a level of control, the NPs were functionalized with light-responsive ligands containing azobenzene moieties. The azobenzene-decorated NPs are stable in toluene for several months under ambient light conditions. In contrast, when exposed to UV light, the NPs self-assembled as a result of the formation of the cis-azobenzene isomer, which is poorly solvated in toluene. During the aggregation of the NPs to form colloidal crystals, surrounding molecules are trapped inside the void spaces between NPs (**Figure 5a**-**b**).

Interestingly, the authors showed that the molecules trapped in these cavities undergo chemical reactions with increased rates and with significantly different stereoselectivity, as compared to those observed in bulk solution. Finally, the irradiation with visible light induces the formation of the trans-azobenzene isomer, leading to disassembly of the aggregates and release of the trapped molecules. This strategy was shown to work with different types of NPs, including Au, Fe_3O_4, and SiO_2.

One could state that this strategy has two important disadvantages, which largely limit its application in various fields, importantly including biological and medical processes. First of all, it could only be implemented in organic solvents such as toluene. Second, the colloidal crystals formed during the aggregation process were very heterogeneous in size. However, an alternative approach was reported more recently, which overcomes these limitations, wherein the hydrophobic effect drives the spontaneous formation of porous water-soluble spherical assemblies of 200 nm in diameter.[63] The assemblies were synthesized by adding hexanethiol to polyoxometalate-protected 4 nm Au NPs, so that alkyl and alkylaromatic molecules were trapped during this process, inside the void spaces between NPs (**Figure 5c**-**d**). Notably, each 200 nm sphere was claimed to trap up to two million hydrophobic guests, meaning that they can host at least five orders of magnitude more hydrophobic guests than the individual supramolecular containers. Additionally, guest molecules could be released in the presence of organic solvents such as methylene chloride, owing to the loss of the hydrophobic effect.

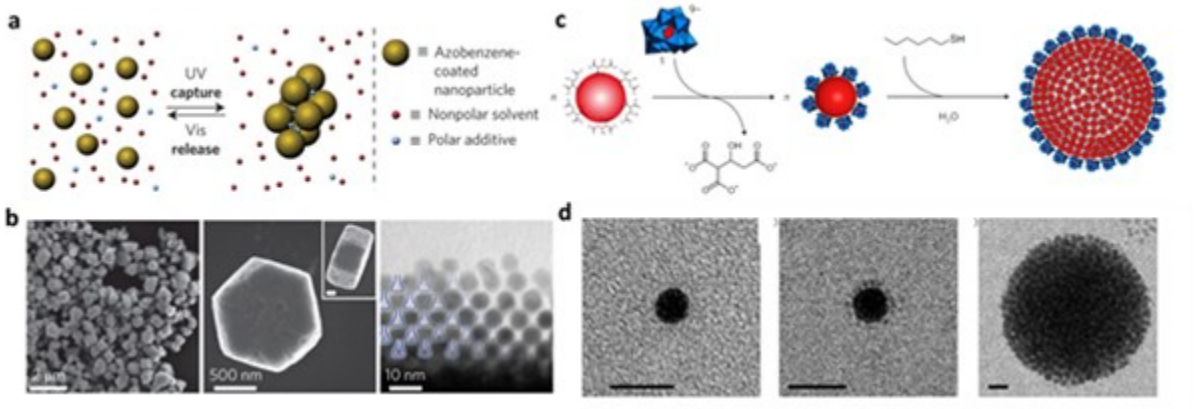

Figure 5. a) Schematic representation of the reversible trapping of molecules during light-induced self-assembly of NPs. b) TEM images (at different magnifications) of colloidal crystals prepared by exposing 6 nm Au NPs to ultraviolet light (scale bar in the inset, 200 nm). Reproduced with permission.[62] Copyright 2016, Nature Publishing Group. c) Synthesis of water-soluble spherical assemblies of 200 nm in diameter using hexanethiol to polyoxometalate-protected Au NPs of 4 nm. d) Cryo-TEM images of the initial citrate-protected Au NPs, the polyoxometalate-protected Au NPs and the 200 nm spherical assemblies. Scale bar, 10 nm. Reproduced with permission.[63] Copyright 2016, Nature Publishing Group.

3. Plasmonic nanoparticles carrying and replicating biomolecules

Surface ligands on NPs are of significant relevance toward their synthesis and functionality. Biomolecules typically carry a variety of active groups, such as –SH, -COOH, -NH_2, -OH etc. Such functional groups not only enable biomolecules to readily adsorb on the NP surface, but also provide the ability to direct the assembly of NPs into well-defined structures. The unique molecular recognition features of biomolecules enable the fabrication of NPs with functional morphology and

anticipated properties. By controlling the amounts and the position of biomolecules on each NP, assemblies with different geometric structure can be obtained, which further exhibit interesting optical and electrochemical properties. Biomolecule-driven nanostructures could be separated or assembled by exploiting the specific recognition of biomolecules, thereby generating changes in their optical activity. Such bio-responsive NPs promise various applications toward biosensing and bioimaging. This section is divided in three parts based on the kind of biomolecule used in combination with the NPs: DNA, aptamers or peptides/proteins.

3.1 NPs carrying DNA

Due to the large number of examples that combine plasmonic NPs with DNA, this section is further subdivided into three parts according to the role that DNA plays in each case: controlling NPs growth, guiding the assembly of NPs or acting as a substrate for the polymerase chain reaction.

3.1.1. DNA surface ligands controlling NPs growth

DNA is composed of four types of nitrogen bases (cytosine [C], guanine [G], adenine [A] and thymine [T]), each with different affinity for metallic surfaces. Therefore, DNA can be used as a programmable code to control NPs growth. For instance, when Au nanoprism seeds were grown in the presence of different homo-oligomeric DNA sequences (e.g., A30, T30, G20, and C30), different shapes such as nonagon, hexagon, and six-pointed stars were obtained due to the different binding affinity, mobility and length of the DNA chains.[64] Importantly, this strategy could be also performed to control the formation of bimetallic plasmonic NPs, which usually show interesting and synergic physical and chemical properties due to the presence of two different metals in their structure. In particular, when palladium nanocubes were used as seeds, rhombicuboctahedron were obtained in the presence of homo-oligomeric DNA chains, with high affinity for the Pd surface (A10), while core-

frame structures were the product when low affinity DNA chains (T10) were added in the overgrowth step.[65] However, despite these examples, the application of DNA-guided synthesis to control the morphology of NPs is still challenging, particularly in the case of multi-metallic NPs.

3.1.2. DNA surface ligands guiding NP assembly

DNA molecules are particularly attractive linkers for the fabrication of versatile NP assemblies because of the encoded base sequences, the tunable length matching the NP size and the unique principle of canonical Watson−Crick base pairing. DNA can be modified on the surface of NPs at designed numbers and specific sites. The density of DNA on the NPs surface can determine the growth of smart NPs, the spatial nanostructure of assemblies, as well as the number of assembled NPs. Although challenging, the modification of DNA on selected sites of anisotropic NPs is critical toward the fabrication of assemblies with desired NP arrangements. The binding sites for DNA on anisotropic NPs have been controlled by blocking the irrelevant sites or by introducing DNA origami as an assembly template. For example, the presence of cetyltrimethylammonium bromide (CTAB) as the coating agent for Au NRs enabled the preferential binding of DNA on the tips,[66] because CTAB can form a packed bilayer on the side faces of NRs, leaving the NR ends more exposed.[67] Interestingly, the same approach can be also applied to selectively bind thiolated single-stranded DNA on the side of Au NRs, in this case dithiothreitol (DTT) and thiol polyethylene glycol (PEG) were used to block the end facets of Au NRs. The subsequent addition of thiolated single-stranded DNA resulted in preferential attachment of DNA on the Au NR side.[68] An additional and more general blocking strategy has been recently reported based on a diblock copolymer (polystyrene-b-polyacrylic acid) to tune the interfacial energies (**Figure 6a**) and achieve regioselective surface encapsulation of NPs. As expected, only the non-encapsulated NP surface could interact with thiolated single-stranded DNA. This strategy can be used to cover only a half of a nanosphere, the side or the end of NRs, the tips and surface of nanoprisms and the center of facets or the vertices of

nanocubes. After DNA capping, it is possible to fabricate a wide range of distinct nanoassemblies, such as dimers and trimers of nanospheres, nanosphere-nanorod dimers and trimers, NP-NR oligomers, NR dimers and trimers, etc.[69]

Although blocking strategies have been very successful to design simple NP assemblies based on the recognition properties of DNA chains, the main revolution in this field has undoubtedly been the DNA origami technology. DNA origami consists of well-defined two- and three-dimensional nanoscale structures formed by DNA, taking advantage of the folding properties of this biopolymer.[70] This technology enables a precise control on the assembly of NPs, as the shape of DNA linkers can be assembled into special conformation (such as linear, Y shape, pyramids, nanocages, nanorings etc.),[71] further determining the geometry of NP assemblies. Over the last decade, the use of DNA origami assembly for NPs has led to a large number of applications, the most important being SERS and chiroplasmonic sensors.

As it was previously discussed, the reproducibility and intensity of SERS signals is related to the homogeneity and the size of inter-NP gaps, and DNA origami allows for a precise control of such gaps. It is therefore not surprising that this technology was applied to improve the performance of SERS sensors. In a recent example, a DNA origami assembly of Au NPs comprising a six helix nanotube bundle was used to attach four Au NPs with an interparticle spacing of 2 nm. The assembly was subsequently attached to silicon nanowires to be used as an optical amplifier for SERS detection.[72] It is worth noting that, since the SERS enhancement factor varies inversely with gap size[73] the design of assemblies with short distances between plasmonic NPs has received considerable attention. By using DNA origami templates, the gap size between 40 nm Au NPs could be tuned down to 1–2 nm, taking advantage of the optothermal-induced shrinking of DNA due to the heat released by plasmonic NPs under laser irradiation.[74]

An additional advantage of DNA origami-guided assemblies is the inherently dynamic nature of DNA, so that such assemblies can be designed to be responsive toward stimuli that can induce conformational changes on the origami. For example, a heavy metal ion sensor was described in which Au NPs bearing different Raman reporters and thiolated single-stranded DNA on their surfaces were reversibly assembled into DNA origami trimers, only in the presence of Hg^{2+} or Ag^{+}. Thus, different enhancements of Raman reporters allowed for simultaneous detection of silver and mercury ions.[75]

Regarding chiroplasmonic sensors, most of the currently available stimuli-responsive, origami-guided assemblies of NPs are based on plasmonic circular dichroism (CD), due to its high sensitivity to detect conformation changes. When plasmonic NPs are arranged in a chiral conformation and in close proximity, their plasmons can couple, giving rise to intense plasmonic CD signals.[76,77] Importantly, plasmonic origami can usually undergo small conformational changes as a response to external stimuli, which induce large variations in the CD spectrum. Jiang et al. exploited this effect to design L-shaped Au NR dimers assembled on diamond-shaped DNA origami templates displaying chiroplasmonic signals. The structure of such an assembly can reversibly change with pH, resulting in variation of the plasmonic CD signal.[78] This sensitivity towards the external environment renders chiroplasmonic sensors ideal for biological applications. A pioneering work in the biological application of chiral NP assemblies was the design of DNA-bridged chiral NP dimers that enable monitoring of their internalization by cells, thereby distinguishing extra- vs. intra-cellular localization in real-time. These dimers spontaneously undergo twisting motion around the DNA bridge, due to changes in electrostatic repulsion after cell internalization, which leads to variations in the intensity and the sign of the CD peaks (**Figure 6b-d**).[79] Although chiral plasmonic assemblies have been mainly used as sensors, it is worth noting that they also show high photocatalytic activity under

circularly polarized light irradiation, for the generation of singlet oxygen.[80] This property was used to accomplish chiroplasmonic photodynamic therapy, mediated by chiral plasmonic dimers.

In addition to the stimuli-responsive behavior of origami-guided NP assemblies towards environmental changes, these assemblies are also potential candidates to detecting nucleic acids, owing to their specific interaction with the DNA origami scaffold. This property has been recently applied to the detection of microRNAs, which are biomarkers for several diseases such as cancer, using a highly-sophisticated origami combining plasmonic and up-conversion NPs, assembled in a pyramidal DNA origami. The assembly displays double optically activity, with strong plasmonic CD and high luminescence, so that microRNA concentration can be monitored using both techniques. Detection is based on origami dissociation in the presence of the target microRNA, which results in a decrease of the plasmonic CD signal and an increase in luminescence intensity.[81]

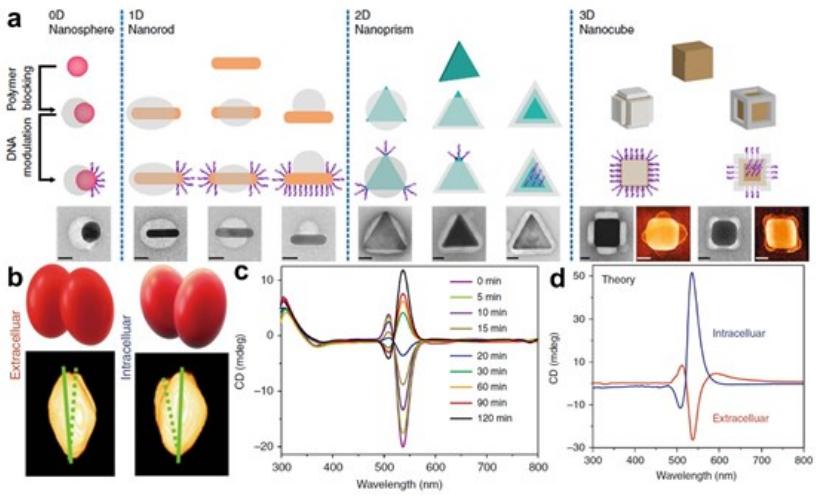

Figure 6. a) Schematic illustration of the selective blocking of NPs for the modification of DNA on regioselective sites. Reproduced with permission.[69] Copyright 2019, Nature Publishing Group. b) Schematic illustration and TEM tomography of DNA-bridged chiral NP dimers outside and inside cells. c) Dynamic CD spectra of dimers incubated with HeLa cells for 2 h. d) Calculated CD spectra of dimers outside and inside cells. Reproduced with permission.[79] Copyright 2017, Nature Publishing

Group.

3.1.3. Polymerase chain reaction guiding NPs assemblies

Primers (short single strands of DNA) can guide the extension and amplification of DNA in the presence of DNA polymerase and nucleotides. This reaction has given rise to the technique known as polymerase chain reaction (PCR), which allows to exponentially amplify a single copy of a DNA sequence.[82] PCR provides a simple and efficient route for the programmable preparation of assemblies from plasmonic NPs,[83] and other types of NPs.[84,85] The general procedure starts with NPs decorated with DNA primers on their surface, and automated PCR is then applied with repeating denaturation, annealing, and extension steps. PCR parameters such as number of cycles, amount of primers per NP and number and size of templates can be used to control the geometry of NP assemblies. For example, lower PCR cycles produce typically NPs dimers, trimers, and oligomers, whereas high PCR cycles give rise to very complex agglomerates. Therefore, by using computerized program control and sophisticated NP modification, assembled superstructures can reach extremely high complexity.

Based on this tunable fabrication method, chiroplasmonic and SERS activity of the obtained plasmonic assemblies can be readily tailored. For example, Kotov, Xu, and coworkers observed that PCR assembled side-by-side Au NRs can be used to detect DNA sequences, with a limit of detection in the attomolar range by using their chiroplasmonic properties. Interestingly, the end-to-end analog showed lower chiral activity (**Figure 7a-b**). [86] Additionally, the same group studied the chiroptical activity of core–shell NP heterodimers formed by PCR with shells of different composition and thickness. The authors reported that shell type and thickness control the position and intensity of the CD bands, respectively. Additionally, the chiroptical activity showed a large enhancement, with a

maximum anisotropy factor of 1.21×10^{-2} upon deposition of gold or silver over the heterodimers (**Figure 7c-d**).[87] Using these dimers, long DNA strands can be detected in the zeptomolar range.

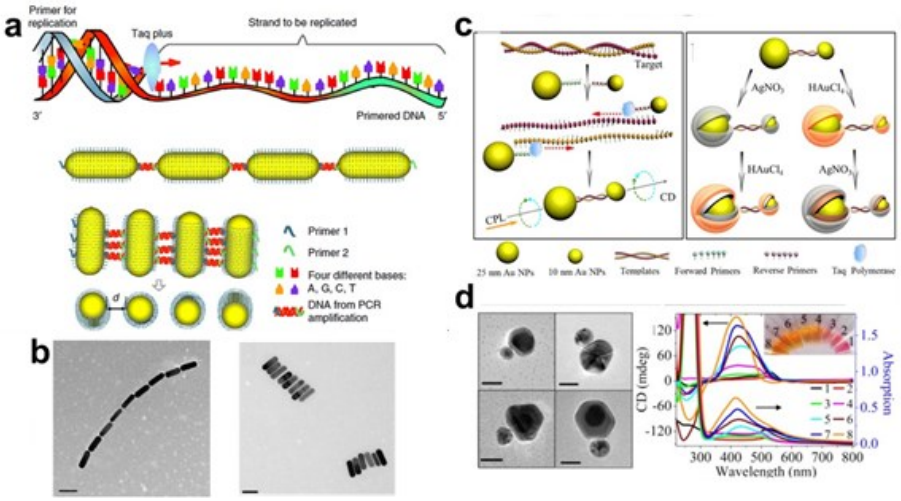

Figure 7. a) Schematic illustration of Au NR assemblies formed by PCR. b) TEM images of end-to-end (upper) and side-by-side (down) Au NR assemblies. Reproduced with permission. [86] Copyright 2013, Nature Publishing Group. c) Schematic illustration of Au NP dimers assembled by PCR and subsequent shell deposition. d) TEM images and CD spectra of Au NP dimers after Ag shell deposition. 1–13 correspond to Au NP dimers after deposition using 0, 5, 10, 20, 30, 50, 70, and 100 µL of 1 mM $AgNO_3$ solution. Reproduced with permission.[87] Copyright 2014, American Chemical Society. <qry>In Figure 2d, should the caption read 1–8 instead of 1–13?</qry>

3.2 Supramolecular structures from NPs functionalized with small biomolecules

Like DNA, peptides can be also applied to control the growth of NPs. The main advantage of peptides over DNA is the abundant number of amino acids with different functional groups in their side

chains, as well as the availability of both enantiomers for each amino acid. Due to these reasons, peptides have attracted the attention of researchers for the preparation of NPs with different shapes. Thiol-containing peptides are the most attractive candidates for the growth of plasmonic NPs, owing to the high affinity of thiols for gold and silver surfaces.[88] In particular, cysteine (Cys) and glutathione (GSH) are the most commonly used peptidic molecules for the preparation of functional NPs, where they can act as templates or reducing agents.[89] It has been recently reported that the chirality of amino acids can be transferred onto NPs during their synthesis. In order to achieve this transfer, small quantities of Cys or GSH were used in the presence of octahedral and cubic gold seeds. These chiral molecules interact preferentially with a certain kind of chiral components at the inorganic surface of the seed (R-/S-kink sites), leading to asymmetric evolution of the NP growth and formation of helicoidal morphologies (**Figure 8a**).[31] The resulting chiral NPs were shown to display a particularly strong chiral plasmonic optical activity, with g factors as high as 0.2. Interestingly, this effect is not only limited to plasmonic NPs, as it has been proven that other NP types can also be prepared using amino acids and peptides to induce chirality. This is the case of chiral CdTe NPs, which were used as mimic of a restriction endonuclease by the generation of reactive oxygen species under photonic excitation (**Figure 8b**).[90]

Peptides have been also widely used for the preparation of supramolecular nanostructures, based on their tendency to self-assembly.[91] Well-defined peptidic nanostructures can be used as templates to obtain NPs assemblies in two different ways. The first strategy consists of growing the NPs over peptidic assemblies, taking advantage of the affinity between the metal salts and peptidic chemical moieties. Tian et al. designed cysteine-modified peptides that assemble into nanotubes and platelets, which can then interact with gold salts. When gold NPs were grown in the presence of the supramolecular assemblies, organized one-dimensional and two-dimensional Au NP arrays were obtained.[92] The second strategy comprises the direct addition of NPs over the peptide

nanostructures. An appealing example of this strategy was used to detect amyloid fibrils using Au NRs. In this study, it was found that Au NRs could readily adsorb onto helical protein fibrils, giving rise to intense chiroptical activity, while they did not interact with monomeric peptides.[93]

Regarding smart NPs assemblies based on proteins, the most commonly used is arguably the specific recognition between antibodies and antigens to yield highly specific biosensors.[94] As an illustration, NP heterodimers were built by using antibodies and antigens as recognition units, such that heterodimers exhibited chiroptical activity, which could be applied to detecting various relevant molecules such as environmental toxins (MC-LR) and cancer biomarkers (PSA).[95] Several examples have been reported regarding the simultaneous functionalization of NPs with DNA and proteins, exhibiting synergistic effects derived from their specific functions. This is the case for a dual functional DNA-protein supramolecular assembly platform formed by a streptavidin protein with four biotin binding sites and biotinylated DNA, which enabled programmable assembly of NPs (**Figure 8c**).[96] By controlling the types and amounts of DNA attached to NPs, a series of assemblies were obtained, including dimers, trimers, tetramers, heterodimers, etc. On the other hand, the chemical anisotropy of proteins, and the versatile chemistry of DNA was used to obtain three-dimensional superlattices made of dimeric Janus NPs, in which the interparticle distances could be tuned.[97]

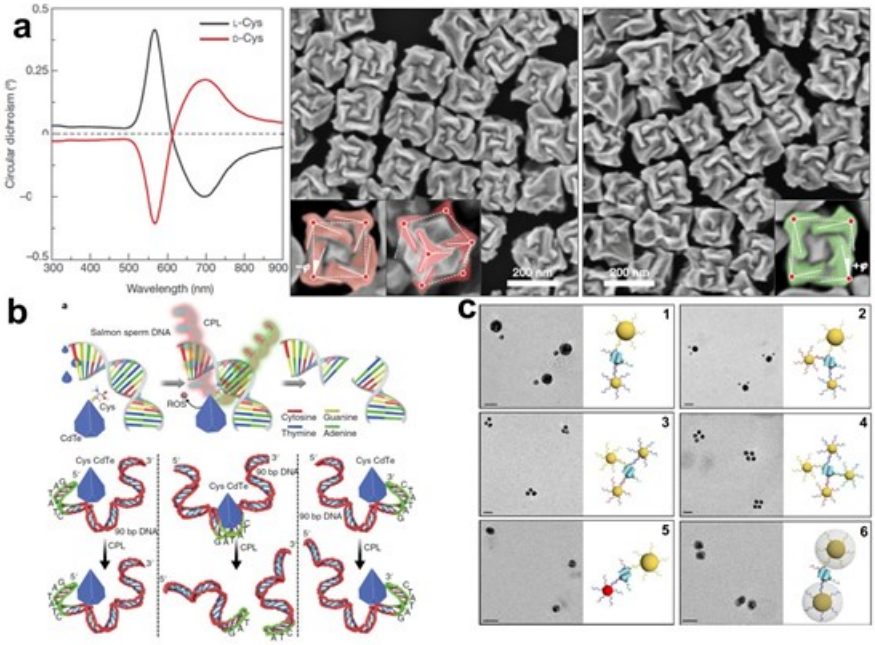

Figure 8. a) Chiral Au NPs synthesized by using L-cys and D-cys as additives: Left, CD spectra; center and right, SEM images. Reproduced with permission.[31] Copyright 2018, Nature Publishing Group. b) Schematic illustration of chiral CdTe QDs for specific DNA cleavage due to generation of reactive oxygen species. Reproduced with permission.[90] Copyright 2018, Nature Publishing Group. c) TEM images of NP assemblies by using DNA-protein supramolecular interactions. Reproduced with permission.[96] Copyright 2019, American Chemical Society.

3.3 NPs functionalized with aptamers

Various types of aptamers have been reported, which target heavy metal ions (Pb^{2+}, Hg^{2+}, Ag^{2+}), biotoxins (MC-LR, OTA, AFB1), disease biomarkers (AFP, CEA, PSA, HER2), etc.[25] The unique affinity toward specific targets enabled aptamers to become a suitable alternative recognition unit for application as biosensors. The competitive affinity between targets and the complementarity for

aptamers has been employed to detach aptamer modified NPs from substrates or to dissociate assemblies, resulting in changes of their optical and electrochemical properties. A relationship could thus be established between the concentration of targets and signal changes.

Aptamers can be easily functionalized on the surface of plasmonic NPs, following the same modification steps developed for DNA. The number and location of aptamers can be controlled upon optimization, which can be used for producing various architectures, including dimers,[98] trimers,[99] tetramers,[100] etc. Aptamer driven nanostructures displayed high yield (e.g. 80%) by designing and selecting the hybridization sequences. At the same time, the hybridized aptamers bound to NP assemblies still exhibited excellent affinity towards their targets, resulting in high detection sensitivity (attomolar level).[99] Various sensors have been reported, based on aptamers, for the sensitive detection of metals in vitro, mediated by SERS or colorimetric methods.[101,102] NPs coated with aptamers usually display high colloidal stability, and can thus be applied to the detection of metals in complex biological media. Gao et al. reported the simultaneous quantitative detection of multiple divalent metal ions in living cells, based on metal-dependent DNAzymes, which are a special kind of aptamer that can drive catalytic reactions by interacting with a specific metal. The authors used chiral satellite assemblies formed from DNAzymes, platinum-coated Au NR (AuNR@Pt) dimers and up-conversion (UP) NPs (**Figure 9a**). Such a complex system needs to be activated by circularly polarized light, which is transformed into heat by the NP assembly, leading to the activation of metal-dependent DNAzymes. When the specific metal for the DNAzyme is present, the enzyme releases a specific dye or UPNPs, which is quenched by AuNR@Pt (**Figure 9b**), allowing in situ bioimaging.[103] Aptamer driven AuNR@Pt dimers showed good stability and did not aggregated in cell culture media for 48 h. Such assemblies also had low cytotoxicity and would not affect the cell viability.

Aptamer driven NP assemblies could also be applied toward the accurate detection of disease biomarkers and circulating tumor cells (CTCs) in serum samples. In order to achieve the practical application of biomolecule-NP assemblies in complex biological media, polymers such as polyethylene glycol (PEG) and poly(styrene-b-acrylic acid) (PS-PAA) have been used as coating agents, to increase stability and resistance to disturbances.[104,105] Thiolated PEG has been applied to the stabilization of plasmonic metal NPs,[106] whereas maleimide-PEG could be used as stabilizing agents for the modification of UCNPs.[107] A bifunctional pPEG (NH_2 -PEG-SH) was also devised to cover the surface of NP assemblies and enhance their biocompatibility in complex biological media.[108] PS-PAA pairs were designed to coat on the surface of Au NR dimers, thereby enhancing intracellular stability and biocompatibility.[109] For example, aptamer-modified Ag NPs were inserted in the structure of Au NP pyramids, for the accurate detection of vascular endothelial growth factor (VEGF) in human serum.[110] The effect of cell culture fluid and fetal bovine serum on the NP assemblies was also evaluated, and no changes in the nanostructures stability was observed under these conditions. Zhao and co-workers went a step further by using chiral Ag@Au core–shell NPs to discriminate CTCs that overexpress human epidermal growth factor receptor 2 (HER2) in human serum, which is a relevant biomarker found in a subtype of breast cancer. The effect of cell culture fluid and fetal bovine serum on the NP assemblies was also evaluated, observing no changes in the stability of the nanostructures under these conditions. Zhao and co-workers went a step further by using chiral Ag@Au core–shell NPs to discriminate CTCs that overexpress human epidermal growth factor receptor 2 (HER2) in human serum, which is a relevant biomarker found in a subtype of breast cancer. When HER2 is present in the dispersion medium, the chiral signal of this assembly decreased due to dissociation of the assembly, in correlation with HER2 concentration.[100] Similar to metal detection, aptamers can also be applied to simultaneously detect several disease biomarkers, due to their high selectivity toward target molecules. For example, three types of aptamers engineered in

SERS-active Ag pyramids, enabled the simultaneous detection of prostate specific antigen (PSA), Mucin-1 and thrombin (**Figure 9c-d**). In this system, binding of specific biomarkers to the aptamer induces a reduction in the size of the assembly, causing SERS signal enhancement due to shorter gaps between NPs.[111] Importantly, the polymer coating on these NP assemblies endows them with excellent stability, but does not affect their optical properties or the specific affinity of aptamers, which are important for sensitive and accurate target detection in biological systems.

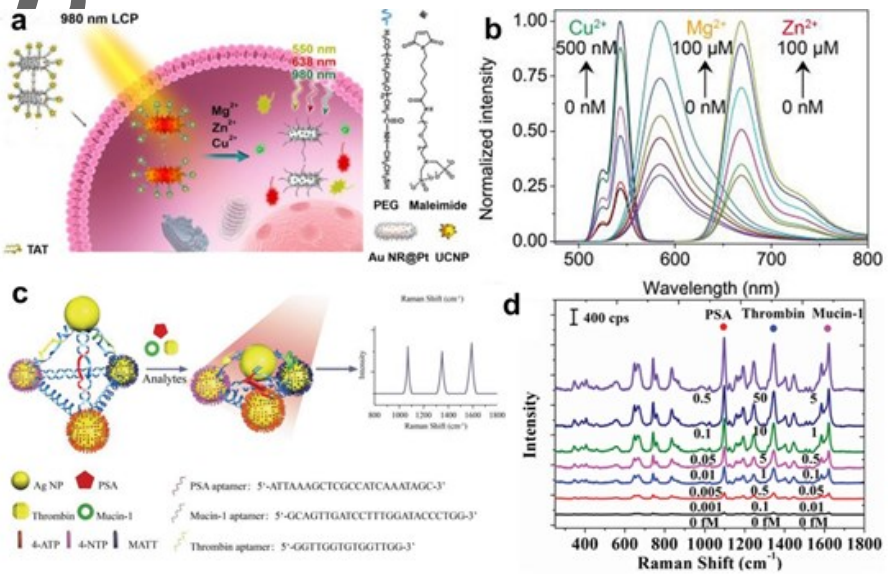

Figure 9. a) Schematic illustration of triple-ion aptamer driven AuNR@Pt dimer-UCNP satellites. b) Fluorescence spectra of assemblies for the simultaneous detection of Cu^{2+}, Mg^{2+} and Zn^{2+}. Reproduced with permission.[103] Copyright 2019, John Wiley and Sons. c) Schematic illustration of three types of aptamer-driven Ag pyramids. d) SERS spectra of Ag pyramids for the simultaneous detection of PSA, Mucin-1, and thrombin. Reproduced with permission.[111] Copyright 2015, John Wiley and Sons.

4. Summary and outlook

The amplitude and scope of NP research science have been immensely expanded by in depth understanding of the mechanisms behind their self-assembly processes.[112] Plasmonic nanomaterials attract increasingly more attention, due to their unique features, including localized surface plasmon resonances, tunable optical properties, high electromagnetic fields, and environmentally friendly character.[113] On the other hand, supramolecular interactions are ubiquitous in nature and in living entities. Over the last two decades, scientists have made significant efforts to understand supramolecular recognition, toward designing optical, biological, catalytic, and other effects. The synergy of supramolecular recognition via biomolecules and synthetic molecular containers can lead to new NP based materials with technological potential in optoelectronics, catalysis, biological sensors, biomedicine, etc.[114] Despite the tremendous progress in NPs assemblies with supramolecular recognition, many challenges and opportunities remain.

Regarding synthetic containers, they have already shown great potential as recognition tools for the design of smart materials. As compared to biomolecules, such containers feature high stability and easy preparation, therefore becoming ideal for the preparation of recyclable and inexpensive sensors. Additionally, their small size, which is similar to the guest size, enables to locate analytes very close to the plasmonic surface, so that the performance of SERS sensors can be highly improved. However, there is still a long way ahead to design synthetic containers that can recognize complex biomolecules with the high affinity and specificity that biological applications require. In the future, better understanding of self-assembly processes might allow the easy preparation of such hosts in a straightforward manner.

Design and synthesis of self-assembling nanomaterials with tailored size and geometry, from plasmonic metals, semiconductors or other tailor-made structures still hold fundamental relevance.

Toward this end, it is essential to develop new strategies to achieve high regioselectivity binding of molecules on NPs surface, thereby well-defined plasmonic assemblies can be obtained. Additionally, the topic of chirality has raised as one of the most popular areas in nanomaterials research.[115] The investigation of chiral nanostructures deepens our understanding of the origin of homochirality in the universe. Although many interesting morphologies of chiral nanostructures have been studied, the interpretation of chirality is still evolving. Computer simulations play an increasingly important role in evaluating dynamics and high-order structures.[116] Importantly, supramolecular interactions offer an effective tool to find analogies with large biomolecules such as nucleic acids and proteins, in terms of their appearance and functions.

Another challenge is to explore superior functions and behaviors of plasmonic nanostructures, which reveal similarities with biomolecules to a greater extent. Plasmonic NPs are not only used to construct high-order nanostructures and hydrogels with excellent optoelectronic or mechanical properties,[117] but are also found to show exciting opportunities in biological applications. For example, endonuclease-like enzymatic activity has been reported in chiral NPs,[90] but the selectivity mechanism still remains elusive. It is worth of study to expand enzyme activity into additional DNA sequences, even including proteins or peptides. Moreover, the inhibition of enzymatic activity, as well as blocking cellular metabolism pathways can also be expected in the future. Due to the outstanding optical and electromagnetic properties of plasmonic materials, as well as the high affinity and specificity derived from synergic effects in biomolecules, we can also envision that biomimetic nanostructures will be further applied to chiral catalysis, environmental monitoring, disease diagnosis, and therapies against severe diseases, such as cancers and neurodegenerative disorders. Photothermal effects from plasmonic NPs offer the possibility to use them for therapeutic purposes, in which specific binding would improve the targeting efficacy of such therapies.[118] These properties will also facilitate structural control over protein corona

formation, which can dramatically alter their biological effects.[15,119] Despite of many reports based on NPs with highly sophisticated designs, we still confront many barriers for practical use, in terms of manufacturing, toxicity, cost, and efficacy.[120–122]

Acknowledgements

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References

[1] V. Myroshnychenko, J. Rodríguez-Fernández, I. Pastoriza-Santos, A. M. Funston, C. Novo, P. Mulvaney, L. M. Liz-Marzán, F. J. G. de Abajo, *Chem. Soc. Rev.* **2008**, *37*, 1792.

[2] A. Furube, S. Hashimoto, *NPG Asia Mater.* **2017**, *9*, e454.

[3] D. J. de Aberasturi, A. B. Serrano-Montes, L. M. Liz-Marzán, *Adv. Opt. Mater.* **2015**, *3*, 602.

[4] M. Rycenga, C. M. Cobley, J. Zeng, W. Li, C. H. Moran, Q. Zhang, D. Qin, Y. Xia, *Chem. Rev.* **2011**, *111*, 3669.

[5] E. Pensa, E. Cortés, G. Corthey, P. Carro, C. Vericat, M. H. Fonticelli, G. Benítez, A. A. Rubert, R. C. Salvarezza, *Acc. Chem. Res.* **2012**, *45*, 1183.

[6] P. Ghosh, G. Han, M. De, C. K. Kim, V. M. Rotello, *Adv. Drug Deliv. Rev.* **2008**, *60*, 1307.

[7] C. L. Nehl, J. H. Hafner, *J. Mater. Chem.* **2008**, *18*, 2415.

[8] M. Grzelczak, J. Pérez-Juste, P. Mulvaney, L. M. Liz-Marzán, *Chem. Soc. Rev.* **2008**, *37*, 1783.

[9] J. Reguera, J. Langer, D. J. de Aberasturi, L. M. Liz-Marzán, *Chem. Soc. Rev.* **2017**, *46*, 3866.

[10] J.-Y. Kim, M.-G. Han, M.-B. Lien, S. Magonov, Y. Zhu, H. George, T. B. Norris, N. A. Kotov, *Sci. Adv.* **2018**, *4*, e1700682.

[11] S. Schlücker, *Angew. Chem. Int. Ed.* **2014**, *53*, 4756.

[12] X. Wang, M. Li, L. Meng, K. Lin, J. Feng, T. Huang, Z. Yang, B. Ren, *ACS Nano* **2014**, *8*, 528.

[13] H. Vanrompay, E. Bladt, W. Albrecht, A. Béché, M. Zakhozheva, A. Sánchez-Iglesias, L. M. Liz-Marzán, S. Bals, *Nanoscale* **2018**, *10*, 22792.

[14] H. Petrova, J. P. Juste, I. Pastoriza-Santos, G. V. Hartland, L. M. Liz-Marzán, P. Mulvaney, *Phys. Chem. Chem. Phys.* **2006**, *8*, 814.

[15] J. Mosquera, I. García, M. Henriksen-Lacey, G. González-Rubio, L. M. Liz-Marzán, *Chem. Mater.* **2019**, *31*, 57.

[16] J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304.

[17] E. Pazos, J. Mosquera, M. E. Vázquez, J. L. Mascareñas, *ChemBioChem* **2011**, *12*, 1958.

[18] V. L. Schramm, *Chem. Rev.* **2006**, *106*, 3029.

[19] M. M. Conn, J. Rebek, *Chem. Rev.* **1997**, *97*, 1647.

[20] D. B. Amabilino, D. K. Smith, J. W. Steed, *Chem. Soc. Rev.* **2017**, *46*, 2404.

[21] J. Y. Nehete, R. S. Bhambar, M. R. Narkhede, S. R. Gawali, *Pharmacogn. Rev.* **2013**, *7*, 107.

[22] A. M. Scott, J. D. Wolchok, L. J. Old, *Nat. Rev. Cancer* **2012**, *12*, 278.

[23] S. Sharma, H. Byrne, R. J. O'Kennedy, *Essays Biochem.* **2016**, *60*, 9.

[24] P. Chames, M. Van Regenmortel, E. Weiss, D. Baty, *Br. J. Pharmacol.* **2009**, *157*, 220.

[25] M. R. Dunn, R. M. Jimenez, J. C. Chaput, *Nat. Rev. Chem.* **2017**, *1*, 0076.

[26] P. Ballester, M. Fujita, J. Rebek, *Chem. Soc. Rev.* **2014**, *44*, 392.

[27] N. A. Kotov, *Science* **2010**, *330*, 188.

[28] J. Song, L. Cheng, A. Liu, J. Yin, M. Kuang, H. Duan, *J. Am. Chem. Soc.* **2011**, *133*, 10760.

[29] E. R. Zubarev, J. Xu, A. Sayyad, J. D. Gibson, *J. Am. Chem. Soc.* **2006**, *128*, 15098.

[30] P. Thoniyot, M. J. Tan, A. A. Karim, D. J. Young, X. J. Loh, *Adv. Sci.* **2015**, *2*, 1400010.

[31] H.-E. Lee, H.-Y. Ahn, J. Mun, Y. Y. Lee, M. Kim, N. H. Cho, K. Chang, W. S. Kim, J. Rho, K. T. Nam, *Nature* **2018**, *556*, 360.

[32] R. Schreiber, N. Luong, Z. Fan, A. Kuzyk, P. C. Nickels, T. Zhang, D. M. Smith, B. Yurke, W. Kuang, A. O. Govorov, T. Liedl, *Nat. Commun.* **2013**, *4*, 2948.

[33] Z. Tang, N. A. Kotov, M. Giersig, *Science* **2002**, *297*, 237.

[34] W. Feng, J.-Y. Kim, X. Wang, H. A. Calcaterra, Z. Qu, L. Meshi, N. A. Kotov, *Sci. Adv.* **2017**, *3*, e1601159.

[35] J. Zhao, M. H. Stenzel, *Polym. Chem.* **2018**, *9*, 259.

[36] D. Dehaini, R. H. Fang, L. Zhang, *Bioeng. Transl. Med.* **2016**, *1*, 30.

[37] A. J. Mastroianni, S. A. Claridge, A. P. Alivisatos, *J. Am. Chem. Soc.* **2009**, *131*, 8455.

[38] S. J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio, O. A. Scherman, *Chem. Rev.* **2015**, *115*, 12320.

[39] N. Hüsken, R. W. Taylor, D. Zigah, J.-C. Taveau, O. Lambert, O. A. Scherman, J. J. Baumberg, A. Kuhn, *Nano Lett.* **2013**, *13*, 6016.

[40] C. Tao, Q. An, W. Zhu, H. Yang, W. Li, C. Lin, D. Xu, G. Li, *Chem. Commun.* **2011**, *47*, 9867.

[41] S. Kasera, F. Biedermann, J. J. Baumberg, O. A. Scherman, S. Mahajan, *Nano Lett.* **2012**, *12*, 5924.

[42] N. H. Kim, W. Hwang, K. Baek, M. R. Rohman, J. Kim, H. W. Kim, J. Mun, S. Y. Lee, G. Yun, J. Murray, J. W. Ha, J. Rho, M. Moskovits, K. Kim, *J. Am. Chem. Soc.* **2018**, *140*, 4705.

[43] R. W. Taylor, R. J. Coulston, F. Biedermann, S. Mahajan, J. J. Baumberg, O. A. Scherman, *Nano Lett.* **2013**, *13*, 5985.

[44] C. Kim, S. S. Agasti, Z. Zhu, L. Isaacs, V. M. Rotello, *Nat. Chem.* **2010**, *2*, 962.

[45] G. Y. Tonga, Y. Jeong, B. Duncan, T. Mizuhara, R. Mout, R. Das, S. T. Kim, Y.-C. Yeh, B. Yan, S. Hou, V. M. Rotello, *Nat. Chem.* **2015**, *7*, 597.

[46] J. Mosquera, I. García, L. M. Liz-Marzán, *Acc. Chem. Res.* **2018**, *51*, 2305.

[47] Y. Han, X. Yang, Y. Liu, Q. Ai, S. Liu, C. Sun, F. Liang, *Sci. Rep.* **2016**, *6*, 22239.

[48] G. Crini, *Chem. Rev.* **2014**, *114*, 10940.

[49] E. M. M. Del Valle, *Process Biochem.* **2004**, *39*, 1033.

[50] D. Wang, W. Zhao, Q. Wei, C. Zhao, Y. Zheng, *ChemPhotoChem* **2018**, *2*, 403.

[51] J. Wu, Y. Xu, D. Li, X. Ma, H. Tian, *Chem. Commun.* **2017**, *53*, 4577.

[52] L. Peng, M. You, C. Wu, D. Han, I. Öçsoy, T. Chen, Z. Chen, W. Tan, *ACS Nano* **2014**, *8*, 2555.

[53] L. Stricker, E.-C. Fritz, M. Peterlechner, N. L. Doltsinis, B. J. Ravoo, *J. Am. Chem. Soc.* **2016**, *138*, 4547.

[54] M. Yamashina, M. Akita, T. Hasegawa, S. Hayashi, M. Yoshizawa, *Sci. Adv.* **2017**, *3*, e1701126.

[55] J. Mosquera, B. Szyszko, S. K. Y. Ho, J. R. Nitschke, *Nat. Commun.* **2017**, *8*, 14882.

[56] M. M. Conn, J. Rebek, *Chem. Rev.* **1997**, *97*, 1647.

[57] E. G. Percástegui, J. Mosquera, T. K. Ronson, A. J. Plajer, M. Kieffer, J. R. Nitschke, *Chem. Sci.* **2019**, *10*, 2006.

[58] D. A. Roberts, B. S. Pilgrim, J. R. Nitschke, *Chem. Soc. Rev.* **2018**, *47*, 626.

[59] J. Rodríguez, J. Mosquera, J. R. Couceiro, J. R. Nitschke, M. E. Vázquez, J. L. Mascareñas, *J. Am. Chem. Soc.* **2017**, *139*, 55.

[60] J. Mosquera, I. García, L. M. Liz-Marzán, *Acc. Chem. Res.* **2018**, *51*, 2305.

[61] J. Mosquera, M. Henriksen-Lacey, I. García, M. Martínez-Calvo, J. Rodríguez, J. L. Mascareñas, L. M. Liz-Marzán, *J. Am. Chem. Soc.* **2018**, *140*, 4469.

[62] H. Zhao, S. Sen, T. Udayabhaskararao, M. Sawczyk, K. Kučanda, D. Manna, P. K. Kundu, J.-W. Lee, P. Král, R. Klajn, *Nat. Nanotechnol.* **2015**, *11*, 82.

[63] Y. Wang, O. Zeiri, M. Raula, B. Le Ouay, F. Stellacci, I. A. Weinstock, *Nat. Nanotechnol.* **2016**, *12*, 170.

[64] L. H. Tan, Y. Yue, N. S. R. Satyavolu, A. S. Ali, Z. Wang, Y. Wu, Y. Lu, *J. Am. Chem. Soc.* **2015**, *137*, 14456.

[65] N. S. R. Satyavolu, L. H. Tan, Y. Lu, *J. Am. Chem. Soc.* **2016**, *138*, 16542.

[66] L. Chang, Y. Khan, L. Li, N. Yang, P. Yin, L. Guo, *RSC Adv.* **2017**, *7*, 13896.

[67] J. Gao, C. M. Bender, C. J. Murphy, *Langmuir* **2003**, *19*, 9065.

[68] W. Ma, H. Kuang, L. Xu, L. Ding, C. Xu, L. Wang, N. A. Kotov, *Nat. Commun.* **2013**, *4*, 2689.

[69] G. Chen, K. J. Gibson, D. Liu, H. C. Rees, J.-H. Lee, W. Xia, R. Lin, H. L. Xin, O. Gang, Y. Weizmann, *Nat. Mater.* **2019**, *18*, 169.

[70] S. Loescher, S. Groeer, A. Walther, *Angew. Chem. Int. Ed.* **2018**, *57*, 10436.

[71] A. R. Chandrasekaran, O. Levchenko, *Chem. Mater.* **2016**, *28*, 5569.

[72] A. Moeinian, F. N. Gür, J. Gonzalez-Torres, L. Zhou, V. D. Murugesan, A. D. Dashtestani, H. Guo, T. L. Schmidt, S. Strehle, *Nano Lett.* **2019**, *19*, 1061.

[73] J. M. McMahon, S. Li, L. K. Ausman, G. C. Schatz, *J. Phys. Chem. C* **2012**, *116*, 1627.

[74] S. Simoncelli, E.-M. Roller, P. Urban, R. Schreiber, A. J. Turberfield, T. Liedl, T. Lohmüller, *ACS Nano* **2016**, *10*, 9809.

[75] S. Li, L. Xu, W. Ma, H. Kuang, L. Wang, C. Xu, *Small* **2015**, *11*, 3435.

[76] M. J. Urban, P. K. Dutta, P. Wang, X. Duan, X. Shen, B. Ding, Y. Ke, N. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 5495.

[77] Z. Fan, A. O. Govorov, *Nano Lett.* **2010**, *10*, 2580.

[78] Q. Jiang, Q. Liu, Y. Shi, Z.-G. Wang, P. Zhan, J. Liu, C. Liu, H. Wang, X. Shi, L. Zhang, J. Sun, B. Ding, M. Liu, *Nano Lett.* **2017**, *17*, 7125.

[79] M. Sun, L. Xu, J. H. Bahng, H. Kuang, S. Alben, N. A. Kotov, C. Xu, *Nat. Commun.* **2017**, *8*, 1847.

[80] F. Gao, M. Sun, W. Ma, X. Wu, L. Liu, H. Kuang, C. Xu, *Adv. Mater.* **2017**, *29*, 1606864.

[81] S. Li, L. Xu, W. Ma, X. Wu, M. Sun, H. Kuang, L. Wang, N. A. Kotov, C. Xu, *J. Am. Chem. Soc.* **2016**, *138*, 306.

[82] C. Ding, C. R. Cantor, *Proc. Natl. Acad. Sci.* **2003**, *100*, 3059.

[83] W. Chen, A. Bian, A. Agarwal, L. Liu, H. Shen, L. Wang, C. Xu, N. A. Kotov, *Nano Lett.* **2009**, *9*, 2153.

[84] H. Kuang, S. Zhao, W. Chen, W. Ma, Q. Yong, L. Xu, L. Wang, C. Xu, *Biosens. Bioelectron.* **2011**, *26*, 2495.

[85] W. Ma, H. Yin, L. Xu, L. Wang, H. Kuang, C. Xu, *Chem. Commun.* **2013**, *49*, 5369.

[86] W. Ma, H. Kuang, L. Xu, L. Ding, C. Xu, L. Wang, N. A. Kotov, *Nat. Commun.* **2013**, *4*, 2689.

[87] Y. Zhao, L. Xu, W. Ma, L. Wang, H. Kuang, C. Xu, N. A. Kotov, *Nano Lett.* **2014**, *14*, 3908.

[88] E. Pensa, E. Cortés, G. Corthey, P. Carro, C. Vericat, M. H. Fonticelli, G. Benítez, A. A. Rubert, R. C. Salvarezza, *Acc. Chem. Res.* **2012**, *45*, 1183.

[89] Z. Ma, H. Han, *Colloids Surf. Physicochem. Eng. Asp.* **2008**, *317*, 229.

[90] M. Sun, L. Xu, A. Qu, P. Zhao, T. Hao, W. Ma, C. Hao, X. Wen, F. M. Colombari, A. F. de Moura, N. A. Kotov, C. Xu, H. Kuang, *Nat. Chem.* **2018**, *10*, 821.

[91] N. Habibi, N. Kamaly, A. Memic, H. Shafiee, *Nano Today* **2016**, *11*, 41.

[92] Y. Tian, H. V. Zhang, K. L. Kiick, J. G. Saven, D. J. Pochan, *Chem. Mater.* **2018**, *30*, 8510.

[93] J. Kumar, H. Eraña, E. López-Martínez, N. Claes, V. F. Martín, D. M. Solís, S. Bals, A. L. Cortajarena, J. Castilla, L. M. Liz-Marzán, *Proc. Natl. Acad. Sci.* **2018**, *115*, 3225.

[94] M. Arruebo, M. Valladares, Á. González-Fernández, *J. Nanomater.* **2009**, *2009*, 439389.

[95] X. Wu, L. Xu, L. Liu, W. Ma, H. Yin, H. Kuang, L. Wang, C. Xu, N. A. Kotov, *J. Am. Chem. Soc.* **2013**, *135*, 18629.

[96] Y.-Y. Kim, Y. Bang, A.-H. Lee, Y.-K. Song, *ACS Nano* **2019**, 10.1021/acsnano.8b06170.

[97] O. G. Hayes, J. R. McMillan, B. Lee, C. A. Mirkin, *J. Am. Chem. Soc.* **2018**, *140*, 9269.

[98] F. Gao, L. Liu, G. Cui, L. Xu, X. Wu, H. Kuang, C. Xu, *Nanoscale* **2016**, *9*, 223.

[99] A. Qu, X. Wu, L. Xu, L. Liu, W. Ma, H. Kuang, C. Xu, *Nanoscale* **2017**, *9*, 3865.

[100] Y. Zhao, Y. Yang, J. Zhao, P. Weng, Q. Pang, Q. Song, *Adv. Mater.* **2016**, *28*, 4877.

[101] J.-S. Lee, M. S. Han, C. A. Mirkin, *Angew. Chem. Int. Ed.* **2007**, *46*, 4093.

[102] D. Yang, X. Liu, Y. Zhou, L. Luo, J. Zhang, A. Huang, Q. Mao, X. Chen, L. Tang, *Anal. Methods* **2017**, *9*, 1976.

[103] R. Gao, L. Xu, C. Hao, C. Xu, H. Kuang, *Angew. Chem. Int. Ed.* **2019**, *0*, 10.1002/anie.201814282.

[104] M. Sun, L. Xu, A. Qu, P. Zhao, T. Hao, W. Ma, C. Hao, X. Wen, F. M. Colombari, A. F. de Moura, N. A. Kotov, C. Xu, H. Kuang, *Nat. Chem.* **2018**, *10*, 821.

[105] X. Wu, C. Hao, J. Kumar, H. Kuang, N. A. Kotov, L. M. Liz-Marzán, C. Xu, *Chem. Soc. Rev.* **2018**, *47*, 4677.

[106] C. Hao, L. Xu, W. Ma, X. Wu, L. Wang, H. Kuang, C. Xu, *Adv. Funct. Mater.* **2015**, *25*, 5816.

[107] X. Wu, L. Xu, W. Ma, L. Liu, H. Kuang, N. A. Kotov, C. Xu, *Adv. Mater.* **2016**, *28*, 5907.

[108] M. Sun, A. Qu, C. Hao, X. Wu, L. Xu, C. Xu, H. Kuang, *Adv. Mater.* **2018**, *30*, 1804241.

[109] L. Xu, Y. Gao, H. Kuang, L. M. Liz-Marzán, C. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 10544.

[110] S. Zhao, W. Ma, L. Xu, X. Wu, H. Kuang, L. Wang, C. Xu, *Biosens. Bioelectron.* **2015**, *68*, 593.

[111] L. Xu, W. Yan, W. Ma, H. Kuang, X. Wu, L. Liu, Y. Zhao, L. Wang, C. Xu, *Adv. Mater.* **2015**, *27*, 1706.

[112] N. A. Kotov, *EPL Europhys. Lett.* **2017**, *119*, 66008.

[113] S. Linic, U. Aslam, C. Boerigter, M. Morabito, *Nat. Mater.* **2015**, *14*, 567.

[114] M.-C. Daniel, D. Astruc, *Chem. Rev.* **2004**, *104*, 293.

[115] W. Ma, L. Xu, A. F. de Moura, X. Wu, H. Kuang, C. Xu, N. A. Kotov, *Chem. Rev.* **2017**, *117*, 8041.

[116] S. Dussi, M. Dijkstra, *Nat. Commun.* **2016**, *7*, 11175.

[117] J. Yeom, U. S. Santos, M. Chekini, M. Cha, A. F. de Moura, N. A. Kotov, *Science* **2018**, *359*, 309.

[118] N. S. Abadeer, C. J. Murphy, *J. Phys. Chem. C* **2016**, *120*, 4691.

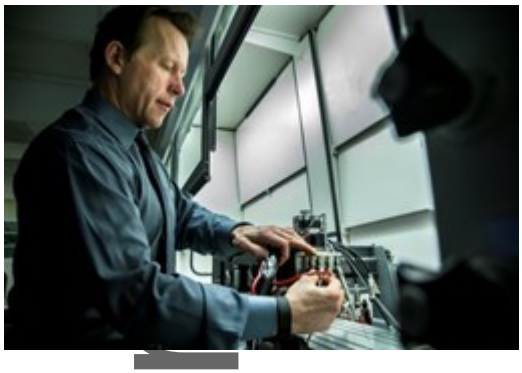
[119] F. Charbgoo, M. Nejabat, K. Abnous, F. Soltani, S. M. Taghdisi, M. Alibolandi, W. Thomas Shier, T. W. J. Steele, M. Ramezani, *J. Controlled Release* **2018**, *272*, 39.

[120] S. Wilhelm, A. J. Tavares, Q. Dai, S. Ohta, J. Audet, H. F. Dvorak, W. C. W. Chan, *Nat. Rev. Mater.* **2016**, *1*, 16014.

[121] C. J. Cheng, G. T. Tietjen, J. K. Saucier-Sawyer, W. M. Saltzman, *Nat. Rev. Drug Discov.* **2015**, *14*, 239.

[122] W. C. W. Chan, *Acc. Chem. Res.* **2017**, *50*, 627.

Jesús Mosquera received his doctorate in 2014 from the University of Santiago de Compostela, Spain, under the supervision of Prof. J. L. Mascareñas. He then undertook postdoctoral studies with Prof. J. R. Nitschke at the University of Cambridge, UK. In 2017, he returned to Spain to join the group of Prof. L. M. Liz-Marzán at CIC biomaGUNE, to work on supramolecular approaches to control cellular uptake of nanoparticles. Since February 2019, he is working as a postdoctoral researcher in the group of Prof. Bert Meijer at Eindhoven University of Technology under the auspices of a Marie Curie fellowship.



Nicholas A. Kotov is working on conceptual foundations and technical realizations of biomimetic nanostructures. In the course of his studies he demonstrated that self-organization is the unifying property of all nanoscale matter. Examples of biomimetic nanostructures associated with his works include graphite oxide, graphene- and clay-based layered biomimetic nanocomposites, chiral nanomaterials, and omnidispersible colloids. His contribution to technology includes ultrastrong nacre-mimetic nanocomposites, soft neuroprosthetic implants, 3D tissue replicas for drug testing, chiral biosensors, and cartilage-like electrolytes for batteries. He is a founder of several startup companies that commercialized bioinspired nanomaterials for biomedical, energy, and automotive technologies.

Luis Liz-Marzán is Ikerbasque Professor and Scientific Director of CIC biomaGUNE in San Sebastián (Spain), since September 2012. He graduated in Chemistry from the University of Santiago de Compostela, was postdoc at Utrecht University, and then professor at the University of Vigo (1995–2012). He has been an invited professor at several research institutions worldwide. His major research activity is devoted to understanding the growth mechanisms of metal nanocrystals, tailoring their surface chemistry, and directing their self-assembly. He also works on the design of biomedical applications based on the plasmonic properties of well-defined metal nanoparticles and nanostructures.

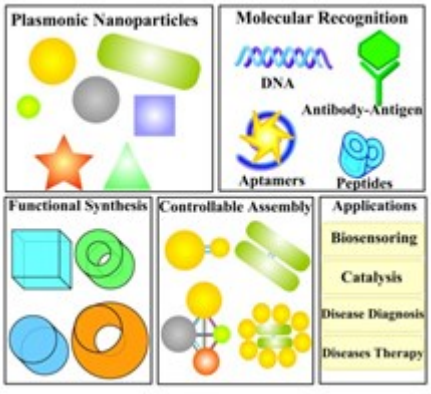
<qry>As per journal guidelines, awards and achievements have been omitted</qry>

Supramolecular interactions are ubiquitous in nature and have inspired scientists to design nanostructures with biomimetic properties, regulated by surface-coating ligands. This paradigm has given rise to multiple studies from the design of molecular containers and enzyme-like catalysts to chiroplasmonic assemblies. Further studies are expected toward chiral catalysis, environmental monitoring, disease diagnosis and therapy.

Plasmonic Nanoparticles

Plasmonic Nanoparticles with Supramolecular Recognition

J. Mosquera, Y. Zhao, H.-J. Jang, N. Xie, Chuanlai Xu, N. A. Kotov, L. M. L.-M.*



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