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**Smart multifunctional nanoparticles design as sensors and drug
delivery systems based on supramolecular chemistry**

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Abstract

Supramolecular chemistry is a well-known field that, applied to analytical chemistry gives, as a result, supramolecular analytical chemistry. Based in its interactions, this field is part of a new area of nanomedicine, called supramolecular medicine. In order to improve the detection of biological molecules to be applied in cell tracking, health problems and biological events, supramolecular chemistry has lately been combined with supra-nanostructures design. In other words, supramolecular systems can be used as tools in the nano-design of nano-systems for the bio-recognition of biological events, host of ions and organic molecules with different structures and intrinsic chemical properties, as enhancer of the solubility, modification of surface properties, bioconjugation for the nanoparticles design, etc. The versatility of these types of systems is very wide; specifically their use in the nanosensor design using nanoparticles was not highly applied. However, in the last years, the bioconjugation of supramolecular systems, such as macrocycles and antibodies, proteins etc. with metallic and polymeric nanoparticles has increased, as well as the development of supramolecular nanoparticles based on host guest interactions of macrocycles. Therefore, this review focuses on the application of supramolecular systems as signal transducers in the nanosensors design for bio-recognition events, detection of biological targets, and drug delivery system. These nanosystems, as transducer hosts and building blocks, are linked to metallic and polymeric nanoparticles; and organize molecular systems for different applications.

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1. Introduction

Supramolecular chemistry¹ is defined as the chemistry of non covalent interactions by the 1987 Nobel prix winner Jean Marie Lehn². These interactions can be used to form nano assemblies and new nanomaterials applied to biomedical, pharmaceutical and analytical determinations. Weak interactions, as van der Waals and strong interactions as ion dipole, dipole-dipole, ionics, and hydrogen bonds will have a great impact over the properties of Nanomaterial. Hence, controlling the building blocks that are part of the supramolecular system will be the macromolecule architecture, associated to specified application, as functional supramolecular systems.³ Looking for a signal transducer in the nanosensor architecture, the best known property of supramolecular hosts is the availability of a defined nanocavity which permits to form host-guest complexes. These host-guest complexes, can modify the spectroscopic characteristics of the guest included into the host cavity, increasing the fluorescent signal, and can contribute in the development of chemosensors, nanosensors and bioprobes.⁴ Moreover, these supramolecular complexes can increase the solubility of the included organic guest, acting as drug delivery systems.⁵ Joining these properties to metallic and polymeric nanoparticles, multifunctional nanoparticles can be designed. For example, linking supramolecular systems to metallic nanoparticles, the included guest will show an enhanced signal due to metal enhanced fluorescence (**MEF**)⁶, surface raman enhanced scattering,⁷ modified electrochemical signals,⁸ and other spectroscopic methods, depending of the guest intrinsic properties. Besides, if these building blocks are part of the nanostructure core, they could design supramolecular nanoparticles⁹ with application

in nanoimaging,¹⁰ cell¹¹ and molecular tracking¹² for developments of new analytical methods.

Supramolecular chemistry is the field where structures, emulated from nature, should contribute to our society with a huge number of applications in different areas of science. For this reason, there are a large number of publications about nanomaterial developments, based on this field.

Moreover it should be mentioned the Nobel Prize in Chemistry 2016 shared between Jean-Pierre Sauvage¹³, J. Fraser Stoddart¹⁴, and Ben L. Feringa¹⁵, due to their work on mechanically interlocked molecules, where supramolecular chemistry takes an important role to build molecular machines.

Due to that organized systems and macrocycles chemistry have a great development, but they are not the only supramolecular systems applied to Nanosensors design, it should be also discussed linear supramolecular arrays as the DNA double strand interactions, specific recognition from antibodies interactions, and non-covalent interactions from biomolecules for targeted applications.

This review specifically focuses on the application of supramolecular systems as very important functional building blocks of the whole structure, tools for nano-architectures, signal enhancers, signal transducers, in nanosensors and nanodevices designs; joined to the properties of metallic nanoparticles, polymeric nanoparticles, molecular organized systems like micelles and vesicles, for bio-recognition events, detection of biological targets, and drug delivery nanosystems. Furthermore, it shows the importance of the supramolecular systems bioconjugated over metallic surfaces for the nanoparticle properties tuning, in order to obtain supramolecular, biodegradable,

multifunctional nanoparticles and new photonic hybrid supramolecular nanomaterials, as well as the interaction between them, their intrinsic properties, and their final nanomaterial properties. Moreover, it is showed the importance of the control of nanoassemblies, nano-aggregation processes and nanoparticle patterns applied as molecular signal transducers. Finally, future trends are discussed in new nanomaterials design for multifunctional nanodevices applications.

2. Design of Multifunctional Nanoparticles as sensors and drug delivery systems.

2.1. Bioconjugation of Supramolecular Systems overMetallic Surfaces

In order to add specific molecular recognition properties, many supramolecular systems can be applied in the nanosensor design. The challenge is to derivatize macrocycles, enzymes, proteins, DNA etc. with functional organic groups for covalent bonding. To link these supramolecular systems as signal transducers on metallic, glass, polymeric surfaces it should be taken into account the chemical structures, host structures and the material surface.

To be bioconjugated, the surface chemistry should have the appropriate organic functional groups: amine, thiol, carboxyl, aldehyde, epoxy, etc., or it can be modified by different methods.¹⁶ Polymeric shells, as the silica ones, applying sol-gel methodologies¹⁷ are very common in literature, as well as organic polymeric shells with micro-emulsion synthetic methodologies.^{18, 19} All macrocycles can be modified, adding linkers to their

structure, to permit the bioconjugation of macrocycles as cyclodextrins²⁰, cucurbiturils²¹, etc.

The cyclodextrin host could be a competitive binding site, as was shown by Kaifer et al.²² The competitive binding of ferrocenemethanol and 1-adamantanol to the CD host immobilized on gold nanoparticles, was studied by electrochemically measurements, showing the thermodynamic stability of the host guest complexes. This work suggests that CD modified gold nanoparticles may be useful as multi-site hosts in aqueous media also applied to analytical applications.

Insert Figure 1

Gold surfaces, grafted with thiolated cyclodextrins were prepared by Kohler et al.^{23,24} Using this gold grafted surface, the inclusion of coumarin nuclei into the cyclodextrin cavity was determined, using time resolved fluorescence anisotropy, second-harmonic generation (SHG), and fluorescence in combination with laser-induced thermal desorption from the surface.

This type of thiolated-cyclodextrin was also linked to other surfaces of metallic nanoparticles, such as palladium and platinum nanoparticles.²⁵

All these different ways of covalent linking over metallic surfaces can be applied to electrode surface modification, with macrocycles as molecular recognition sites. Keyes et al.²⁶ studied self-assembled monolayers (SAMs): the influence of addition of alkanethiol on the Pt electrode surfaces, modified with pyridine functionalized δ -cyclodextrin in order to control the cyclodextrin orientation over the surface, was

developed. Silva et al.²⁷ immobilized cyclodextrin on gold surfaces by chemical derivatization of an 11-amino-1-undecanthiol self assembled monolayer. The redox response had good correlation to the increasement of the hydroquinone oxidation peak. It was essayed for dopamine and, in that case, it did not work, but it could be overcome by improving the design of the device. Willner et al.²⁸ developed a CdS nanoparticle /cyclodextrin-functionalized electrodes for enhanced photoelectrochemistry. This electrode is able to detect methyl viologen in aqueous solutions and the linking strategy, was the well-known boronic acid interaction, with sugar molecules from the cyclodextrins macrocycle.

The adamantane-cyclodextrin complex is a strong and very well known molecular interaction that could be used, forming part of more complex nanostructures.²⁹ An example is applied to the challenging goal for the development of 3-D nanostructure on electrodes surfaces applied to biosensors. Glucose oxidase, modified with cyclodextrins, was attached on adamantane-pyrrole electrochemically polymerized on single walled carbon nanotubes frameworks for the glucose oxidase bioconjugation, applied to glucose detection.³⁰

Other macrocycle receptors as cucurbiturils could also be modified, in order to link them over glass surfaces. Kim et al.^{31, 32} published a facile synthesis of Cucurbituril derivates, with different ring sizes, via direct functionalization on glass surface, modified with thio-organosylanes. Thereby, fluorescent amino compounds can be detected, using fluorescence microscopic imaging. The utility of this grafting of macrocycles, is that it allows the design of patterned fluorescent complexes, linking for sensors and biochip arrays. Optoelectronic detection was developed for saxitocin sensing by Koh et al.³³ A

self-assembled calix [4]arene derivative monolayer as recognition - functional interfaces on gold surface, was fabricated. An interaction study between saxitocin and calix [4]arene derivative monolayer was performed, using surface plasmon resonance (SPR) spectroscopy. Moreover, calixarenes are applied for ion detection; Valeur et al. developed mesoporous silica functionalized by a covalently bound calixarene-based fluoroionophore, for selective optical sensing of mercury (II) in water.³⁴

The combination of optics and supramolecular chemistry allows an enhanced optical signal for organic molecule detection.

There has lately been a great amount of patterning papers and biofunctionalization of surfaces looking for nano-arrays, and supramolecular chemistry plays a very important role in the nano-architecture design. For instance, Huskens et al.³⁵ developed patterning cyclodextrin monolayers on silicon oxide using nanoimprint lithography and its application in 3D multilayer nanostructuring. The method is based in the interaction between the cyclodextrin functionalized nanoparticles (the host), and adamantly functionalized dendrimers. The method can be used to create various composite nanosized building blocks, which have a variety of applications as quantum dot devices, biosensors, and particle based sensors. Metal ions sensing, based on fluorescent SAMs, was developed by Crego-Calama.³⁶ In this sensor surface, an amino-organo-silane was used, to link an ion sensor and a fluorophore (the host-ion interaction modify the fluorescence collected), sequentially. All these examples from the literature show us the importance of linking the knowledge of supramolecular chemistry to surfaces of electrodes, nanoparticles, etc. for the nanodevices development applied to the molecule

recognition. The next section shows application examples of molecule detection and bio-recognition events, using these types of nano-supra-structure design.

2.2. Nano-aggregation as Signal Transducer based on Supramolecular Interactions

Due to the stability of the colloidal systems it is a very important issue for any application, the challenge it is to control the Nanoaggregation and apply this phenomena to obtain information about the state of the molecular system from the non-covalent interactions. Moreover, from these inter-particle interactions modified spectroscopic properties, enhanced plasmonic properties and energy transfer phenomena can be measured.

Macrocycles act as molecular receptors based on their host-guest interactions, to form host guest complexes. Linking macrocycles to metallic and polymeric nanoparticles, in presence of a guest, allows the formation of nano-aggregates that will be identified by spectroscopic techniques, and so, will the indirect molecular detection of analytes. For example, metallic nanoparticles have a characteristic absorption plasmon, depending on the metal, and the colloidal state shows different spectra compared to the aggregate state. Plasmon shift and diminution of the absorbance intensity are measured in the case of aggregation. This phenomenon can be induced and controlled, modifying the nanoparticle surface and controlling the adding of homo-bifunctional arm guests. Kaifer et al.³⁷ demonstrate that gold nanoparticles can be modified with molecular receptors, as cyclodextrins (addition of per-6-thio- β -cyclodextrin)³⁸. They studied the effect of addition of a ferrocene³⁹ dimer that strongly interacts with the cyclodextrin host and acts

as a linker between different gold nanoparticles, leading to the aggregation. Adding the guest dimer, a red shift is observed on the surface plasmon resonance absorption of the colloidal particles, and then, immediately after, a slow precipitation, accompanied by an attenuation of the intensity. Consequently, this nanosystem could be used as a sensor to predict the colloidal state.

Insert Figure 2

The same host-guest strategy was used to prepare interactions between cyclodextrin-gold nanoparticles and ferrocene derivate (alkyldimethyl (ferrocenylmethyl) ammonium ions) to be used as organic-aqueous solvents phase transfer agent.⁴⁰ The structure of the aggregate, formed upon transfer of cyclodextrin capped to the chloroform solution, is postulated to resemble that of reverse micelles. But caused by the polarity of cyclodextrins, it can be applied for stabilisation of nanoparticles in aqueous media.⁴¹ Moreover, the same research group synthesized gold nanoparticles capped with thiolated δ cyclodextrins host that formed large network aggregates in the presence of C_{60} fullerene molecules.⁴² This phenomenon is driven by the formation of inclusion complexes between two cyclodextrins, attached to different nanoparticles and one molecule of C_{60} .

Besides, Forster et al.⁴³ formed a three dimensional assembly of cyclodextrin gold grafted nanoparticles, driven by the interaction with adamantane unit of a redox active metal complex of Osmium. The redox properties and the diffusion, like electron transport dynamics of this gold nanoparticles multilayer, were studied using voltammetry. The homogeneous charge transport diffusion coefficient was 40 fold higher than for a solid

deposit of the cyclodextrin complex alone. The metal nanoparticle appears to promote charge propagation through the assembly.

Not only metallic nanoparticles are used for these nano-supramolecular assemblies. Reinhoudt et al.⁴⁴ developed β -cyclodextrin functionalized silica nanoparticles to form a direct self-assembly, based on multivalent supramolecular interactions with adamantly terminated dendrimer. A good discrimination between dendrimer-covered and uncovered areas of cyclodextrin monolayer substrates was observed, allowing the directed self-assembly of the silica particles onto dendrimer-patterned areas, created by microcontact printing.

Other host-guest interactions could be applied to proteins, as antibody-antigen interactions detection. Gold nanoparticles and grafted biotin were synthesised and aggregation was induced by streptavidin addition.⁴⁵ TEM images and turbidity measurements were done. Using another biotin linking, Pérez-Luna et al.⁴⁶ developed controlled and reversible aggregation of biotinylated gold nanoparticles. The aggregation process was found to be dependent on the streptavidin and biotinylated concentration. A red shift was measured by absorption spectroscopy, without precipitation in the aggregated state. Reversal of nanoparticle aggregation was done by addition of soluble biotin to the streptavidin-nanoparticle aggregates. Murphy et al.⁴⁷ synthesised a preferential end-to-end assembly of gold nanorods by biotin-streptavidin connectors. This strong interaction permits the design of different nano-architectures for nanodevices applications.

There are different metallic nanoparticle functionalization ways to stabilise and link it to other biomolecules, as sugars, to induce the nanoparticle aggregation. For

example, Kataoka et al.⁴⁸ studied a quantitative and reversible lectin induced association of gold nanoparticles, modified with α -Lactosyl- ω -mercapto-poly (ethylene), and Tomoaia-Cotisel et al.⁴⁹ studied the self assembly characteristics of gold nanoparticles in the presence of cysteine.

All this types of approaches can be applied to nanosensor design, to detect organic and biological molecules, ions, etc. Zhang et al.⁵⁰ developed cyclodextrin functionalized silver nanoparticles, for the naked eye detection of aromatic isomers. This nanosensor is based on the cyclodextrin-guest interaction and the isomers structures, which have an influence in the interaction between nanoparticles, and the plasma absorption change, depending on the isomer addition. A similar approach for ions detection was developed by Thomas et al.⁵¹ He reported a synthesis of silver and gold nanoparticles using a bifunctional molecule, namely Gallic acid. This molecule is able to act as a reducer, stabilizer of nanoparticles, and can interact with anions at the same time. From this interaction, different absorption plasmons are generated, depending on the ion and on their concentration.

Biological self assemblies as DNA are used as bio recognition strands that can detect DNA sequences, related to serious health conditions like HIV. A highly selective DNA hybridization assay was developed by Yu et al.⁵², based on surface enhanced Raman scattering (SERS) for DNA sequencing, related to HIV. Silica nanoparticles, grafted with complementary DNA sequences to HIV gene, were synthesised for this purpose. Also, Liu et al.⁵³ synthesised an assembly of DNA functionalized nanoparticles, and studied the effect of alcoholic media in the thermodynamic and kinetic trends for DNA hybridization. This study shows an opposite effect trend for DNA hybridization.

Currently, there is a huge development of these DNA-nanoparticles sensors, not focused in this review, but which should be mentioned. For example, M. Han et al.⁵⁴ synthesised DNA oligonucleotides core-shell silver grafted nanoparticles, applied to DNA quantification, based on colorimetric measurements, permitting detection limits of 100 pM. But even lower LOD by Boudreau et al. was determined by FRET, coupled with MEF based on ultrafluorescents nanoaggregates of silver core-shell nanoparticles.⁵⁵ And, Li et al. has recently demonstrated the influence of the control of nanoaggregates on MEF factor that can arise to 27 times for FITC.⁵⁶

This concept of nanoaggregation and supramolecular interactions, is not only applied to molecular detection, nanoimaging and developments of new analytical methodologies, but is also applied to the synthesis of supramolecular nanoparticles.

2.3. Nanosensors Based on Supramolecular Interactions

Bioconjugating supramolecular systems, as molecular recognition sites and nanoparticles is possible, in order to tune new materials, as nanosensors. Each component of the nanostructure has its properties, producing, as result, a final nanodevice with a specific targeted application. In this section, different examples of nanosensors based on supramolecular systems, are shown. More than 60 % of nanosensors existing in literature, based on linking supramolecular systems on nanoparticles, are done using native and modified cyclodextrins, and the rest calixarenes, cucurbiturils, porphyrins, crown ether (20 %) and others supramolecular systems, as antibodies, or other surface modifications, etc. (20%).

Different nanoparticles can be used depending on the application. Regarding metallic nanoparticles; gold nanoparticles are biocompatible and easily grafted via thiol linkages. Silver nanoparticles show the strongest absorption plasmon, compared to other noble metallic nanoparticles, and can be bioconjugated using organosilane shells (core shell nanoparticles); magnetic nanoparticles can be collected or detected by a magnetic field, etc. Generally, noble metallic nanoparticles can be modified by an organosilane shell⁵⁷, permitting the incorporation of fluorescent molecules. These nanoparticles can be easily tracked, as well as quantum dots. Besides, these types of nanoparticles, tuning the distance between fluorescent silica shell and metallic surfaces, allows measuring metal enhanced fluorescence (MEF).⁵⁸ Also, polymeric nanoparticles can be bioconjugated and can be filled as a cargo for drug delivery applications.⁵⁹

The majority of modified noble metallic nanoparticles presented in literature are with cyclodextrins, due to their easy derivatization.

Silver nanoparticles grafted with per-6-deoxy-(6-thio)- β -cyclodextrin (CD-SH), were applied for sensing of polycyclic aromatic hydrocarbons (PAHs). Cyclodextrins-PAHs nanoparticle complexes can be detected by surface-enhanced Raman scattering (SERS).⁶⁰ In this nanosensor, the metallic surface is stabilized by the modified cyclodextrins, but also metallic nanoparticles can be stabilized synthesizing silica core-shell nanoparticles, thus permitting the biofunctionalisation of silanol groups. Accordingly, X. Gao et al.⁶¹ synthesised cyclodextrin, functionalized superparamagnetic Fe₃O₄/amino silane core shell nanoparticles via layer by layer method. These nanoparticles have recognition sites from the cyclodextrins and respond to an externally

applied magnetic field, their behaviour *in vivo* and *in vitro* can be artificially manipulated.

Gold nanoparticles grafted onto mono-6-thio- β -cyclodextrin, were synthesized, and exploiting the cyclodextrin-nitrobenzene recognition, modified the guest electrochemical signal caused by guest inclusion.⁶² In order to detect dopamine molecules by electrochemical detection, cyclodextrin magnetic grafted nanoparticles were synthesised by Peng et al.⁶³ Cyclodextrin was attached to this nanosensor, by a polyethylene glycol-tosylate activated, and a magnet was used to capture the magnetic nanoparticle cyclodextrin-dopamine complex over the surface electrode.

Insert Figure 3

From another point of view, nanoparticles modified with cyclodextrins can be just platforms to attach natural, and more specific supramolecular systems like enzymes; for example, the immobilization of redox enzymes on cyclodextrin-coated magnetic nanoparticles for biosensing applications.⁶⁴

Likewise, cyclodextrin gold grafted nanoparticles can be used to develop an electrocatalytic glucose sensor. This sensor is formed by a platinum electrode surface, modified with cyclodextrin gold nanoparticles embedded in a glucose oxidase film.⁶⁵ This nano-electrode array acts as an electrode mediator, allowing to shuttle electrons from the redox center of the enzyme to the surface of the working electrode. It reduces the operating potential and enhances glucose selectivity and sensitivity, improving the enzymatic electrochemical detection. As it was shown in the previous example, multilayer nanostructures are applied to nanosensor developments. Protein folding using

metallic nanoparticles can be an interesting field to develop. Uddin et al.⁶⁶ used cyclodextrin magnetic grafted nanoparticles as solid phase artificial chaperone, to assist protein refolding in vitro using carbonic anhydrase bovine as model protein.

A bienzymatic supramolecular nanoassembly, containing catalase and Cu, Zn-superoxide dismutase, was reported by Caballero et al.⁶⁷ Catalase was hydrophobically modified with 1-adamantanecarboxylic acid and then immobilized on β -cyclodextrin coated gold nanoparticles via supramolecular interactions. The bienzymatic nanocatalyst was further prepared by co-immobilization of cyclodextrin modified superoxide dismutase. Superoxide dismutase was 90-fold more resistant to inactivation by 100 mM H_2O_2 , after bienzymatic immobilization with catalase on metal nanoparticles, showing the importance of supra-nano-structures in electrochemical sensors.

Nanoparticles grafted with cyclodextrins, are developed and applied not only to nanosensors, but also to other receptors. Grafted palladium⁶⁸ and platinum⁶⁹ cyclodextrins are applied as catalyst of reactions, gold nanoparticles cyclodextrin grafted onto photo-thermal therapy⁷⁰, biomedical research studies⁷¹ and drug delivery.⁷² Magnetic nanoparticle-supported crown ethers were developed and evaluated as catalysts for solid liquid phase transfer reactions, showing an enhanced catalysis effect.⁷³

Noble metallic nanoparticles grafted with other supramolecular systems as calixarenes, porphyrins, applied to nanosensors design are found in literature, but not so abundantly as what is found in relation to cyclodextrins. Modified calixarenes as p-sulfonylcalixarenes are directly linked over the metallic nanoparticle surfaces due to their electrostatic interactions with silver nanoparticles for organic molecules detection,^{74, 75} or

they can be modified, appending to the aromatic moiety organic reactive linkers, to be attached over magnetic nanoparticles for ion detection.⁷⁶

Fluorescent nanosensors are similarly developed, using modified metallic nanoparticles, polymeric nanoparticles and quantum dots as solid supports for biorecognition supramolecular system grafting.

As regards metallic nanoparticles, Tang et al.⁷⁷ developed a novel assembly complex of gold- β -cyclodextrin-fluorescein, for the fluorescent probing of cholesterol and its application in blood serum. In absence of cholesterol, the gold- β -cyclodextrin-fluorescein complex shows a fluorescein quenched by the metal that is switched off by the cholesterol-cyclodextrin complexation. This phenomenon is explained by the guest induced location change of the fluorescein, from the inside to the outside of the cavity, suggesting that the assembly of gold- β -cyclodextrin-fluorescein complex is an effective fluorescent probe for cholesterol recognition. Similarly, gold nanoparticles can be used as proof of concept of a fluorescent cyclodextrin complex carbonanotube (CNT) nanosensor for proteins detection, where the surface chemistry plays an important role in the supramolecular nanostructure.⁷⁸

Other supramolecular receptors applied to fluorescent nanosensor design over gold nanoparticles, are porphyrins. Lemmetynen et al.⁷⁹ synthesized free-base porphyrins with thioacetate terminated linkers, in different positions, on the porphyrin molecule, and were synthesised and attached to tetraoctylammonium bromide (TOABr) stabilized gold nanoparticles. Fluorescence of porphyrins is observed to be strongly quenched after the attachment to nanoparticles. Fluorescence lifetime of porphyrins functionalized gold nanoparticles was determined to be very short, 3-5 ps, measured by the up conversion

method. The short fluorescence lifetime indicated an efficient energy transfer to the gold cores. Future analytical applications can be done, using these types of grafted nanoparticles supramolecular systems.

DNA oligonucleotides detection can be done using a plasmonic approach as was developed by Lakowicz et al.⁸⁰. Oligonucleotides bound silver nanoparticles were coupled through hybridization with target complementary oligonucleotides. Fluorescence images were monitored by scanning confocal microscopy. Shortened fluorescent lifetimes were measured, indicating that the fluorescence was enhanced via near field interaction mechanism, between the fluorophore and the metal nanoparticle. Moreover, fluorescent metallic nanoparticles applied to cell tracking and molecular membrane surface recognition can be synthesised. Cy5-avidin conjugate bound silver nanoparticles were prepared as a fluorescence molecular reagent for the cell imaging by the same research group,⁸¹ showing the different applications that can be developed, based on these nano-supramolecular systems.

In order to improve for real applications, the methods should not be time consuming, and the biosensing should work with a minimal sample volume. In this way, fluorescent silver core-shell DNA nanoparticles grafted with a fluorescent polymer was developed by Boudreau et al., for DNA detection based on MEF, coupled with FRET and data analysis from nanoimaging, obtained by cytometry and fluorescent detection. With this nanostructure and instrumental set up, it was possible to direct molecular detection of *SRY* gene from unamplified genomic DNA in blood samples.⁸²

Also, the importance of these enhanced fluorescent methods for ion detection, based on supramolecular interaction, should be mentioned, as for example metal-

enhanced fluorescence based calcium detection with an increase greater than 100-fold in signal/noise, using Fluo-3 or Fluo-4 and silver nanostructures.⁸³

Other nanoparticles as polymeric ones can be synthesized, incorporating fluorophores or bio-conjugating fluorescent supramolecular systems. Macrocycles as calixarenes can be derivatized with fluorescent molecules, improving their tracking and detection. Valeur et al,³⁴ synthesized mesoporous silica, functionalized by a covalently bound calixarene-based fluoroionophore, for selective optical sensing of mercury (II) in water. Calixarenes were modified with two dansyl fluorophores, allowing the detection and enhancing the ion fluorescent detection by the quenching of dansyl moiety, induced by mercury ions. These Mesoporous silica nanoparticles were used as support for grafting of the fluoroionophores.

Besides, it should be noted that organized systems, as vesicular surfaces, can also be engineered to be used as fluorescent sensing platforms. Chemosensors based on self-assembled vesicle membranes, modified with transition metal complexes with vacant coordination sites, and luminescent reporter groups, that enable convenient monitoring of ligand-binding events and dyes, were developed by König et al.⁸⁴ This group also developed membrane-embedded luminescent receptors that produced an optical response, based on FRET in the presence of small peptides as external ligands.⁸⁵ Moreover, based on changes of the emission properties, self-assembled phospholipid vesicles were functionalized with binding aptamers for thrombin detection.⁸⁶

These are nice examples of fluorescent nanobiosensors, but a higher volume of publications is found in relation to the use of quantum dots compared with metallic and polymeric nanoparticles and organized systems grafted with supramolecular systems.

Many grafted cyclodextrins quantum dots (QDs) are developed, exploiting the host-guest interactions in order to generate FRET,⁸⁷ quenching and fluorescence enhanced of QDs applied to biosensors design. Liu et al.⁸⁸ synthesised β -cyclodextrin modified CdSe QDs and CdSe-CdS core shell structured. These nanostructures are photo-activated by room light, and the cyclodextrins cavities allow the formation of host-guest complexes, with different organic molecules. The fluorescence of these receptor-modified QDs could be reversible, tuned in two directions, enhanced or quenched by selectively introducing different redox-active substrates in aqueous media. Willner et al.⁸⁹ developed a β -cyclodextrin modified CdSe/ZnS QDs for sensing and chiroselective analysis based on FRET between the QDs and rhodamine B incorporated into the cyclodextrin cavity. This FRET phenomenon is used for the competitive analysis of the following pairs, adamantenecarboxylic acid: p-hydroxytoluene, and D, L-phenylalanine: D, L-Tyrosine. These functionalized QDs are also implemented for p-nitrophenol, using an ET quenching route. Another example of biomolecule sensing are nanoassemblies, combining grafted concanavalin A- quantum dots (Con A, a sugar binding lectin protein with four sacharides binding sites) and cyclodextrin-gold grafted nanoparticles, which was developed by Yu et al. for glucose sensing, with high sensitivity and selectivity in serum samples.⁹⁰

Insert Figure 4

Contaminants as polyaromatic compounds (PAHS) were detected by QDs grafted with cyclodextrins⁹¹ and with calixarenes, developed for Hg^{+2} .detection.⁹² These

examples show the importance and versatility of molecular recognition, joined to nanoparticle properties, opening new possibilities in nanosensors design.

Other architectures are designed in biosensing for molecular detection using macrocycles as host, forming part of membranes and films structures that interact with the targeted molecules. Thus, cyclodextrines,⁹³ crown ether,⁹⁴ calixarenes⁹⁵ and porphyrines,⁹⁶ etc. were used. The specificity of the analytical methods, based on supramolecular interactions is still in discussion, to improve the transduction and enhancement of the signal of detection and quantification of analytes. The evaluation of different analytical techniques and the development of new analytical methodologies should be included.

It must be noted that plasmonic interactions between two nanoparticles generate an electromagnetic hotspot with a high intensity in the near field, and if the dye target interacts into this nanoparticle gap, higher signals based on MEF and SERS effects can be measured. One of the challenges in these nanosystem designs is to put both nanoparticles and analytes on the right place and distance. For this reason, all studies related to the different ways to control these distances and interactions, are highly interesting and of great impact on new analytical developments, as single molecule detection (SMD).⁹⁷

The control of synthetic routes to dimmer and trimmer nanoparticles is not easy, due to all the variables that affect the chemistry of surfaces into colloidal systems. Then, in this challenge, supramolecular chemistry is of great importance in the nanostructure for specific and controlled interactions between nanoparticles. A. V. Veglia, and E. A. Coronado groups had designed stable small colloidal SERS substrates based on cucurbit

[6]uril host guest interactions for Ultrasensitive Detection. They were able to control structures higher than 1000 nm nanoaggregates to 100 nm dimmers, just modifying the surface chemistry and host- guest concentration ratios.⁹⁸

2.4.Supramolecular Nanoparticles

In all the examples above mentioned the supramolecular interactions were applied to molecular recognition but it is not the only application. In order to design new Nanoarchitectures based on the supramolecular interactions as building blocks, it could be obtained Supramolecular nanoparticles. These nanoparticles are synthesized from the combination of polymer chemistry, supramolecular chemistry and their interaction, applied to the design of new nanostructures with different applications. The combination of different properties from plasmonics, fluorescence, antibodies interactions, and polymer chemistry, smart nanoparticles with many properties can be designed, to give a final material applied to biodetection.

Fluorescent silica core Nanoparticles modified with supramolecular systems, antibodies and specific biomolecules for targeted applications, as tracking cells and biological events, are of high interest for developments of new Bioanalytical methods.

Most of the current bacterial detection methods are time-consuming and laborious and can detect only one bacterial pathogen at a time. Tan et al. designed fluorescent nanoparticles for multiplexed bacteria monitoring.⁹⁹ These nanoparticles are based on multicolored FRET (fluorescence resonance energy transfer) silica nanoparticles, modified with monoclonal antibodies specific for pathogenic bacteria species *Escherichia coli*, *Salmonella typhimurium*, and *Staphylococcus aureus*. These nanoparticles are rapid,

sensitive, and selective for pathogenic bacteria detection, which is extremely important for proper containment, diagnosis, and treatment of diseases like food borne illness, sepsis, and bioterrorism.

Another nanoarchitecture combining plasmonic, supramolecular, and polymeric properties could be mentioned: optical detection of antibody using silica-silver core-shell nanoparticles.¹⁰⁰ These nanoparticles are formed by a silica core decorated with silver nanoparticles, conjugated with antibodies. The silver grafted nanoparticles show a strong surface plasmon resonance peak at 453 nm that is red shifted in the presence of anti-antibody interactions. In this case, the silica nanoparticle is a solid support for the plasmonics from the supramolecular modified metallic nanoparticles.

Supramolecular systems, as cyclodextrins and cucurbiturils macrocycles can form different material 3-D structures, as shells, based on their host-guest strong interaction, permitting the surface derivatization applied to bioconjugation, nanoparticles stabilisation, etc. Using grafted gold nanoparticles thio-PEG and cyclodextrins hydrophobic interactions, permits adding a crosslinker agent to the core shell nanoparticles synthesis.¹⁰¹

Insert Figure 5

Similarly, an approach to the design and fabrication of mechanized mesoporous silica nanoparticles is demonstrated in the proof of the principle level based cyclodextrins and cucurbiturils, leading to cargo release from the inside of the nanoparticles,¹⁰² based on supramolecular architectures.

Insert Figure 6

Other example of the importance of the cyclodextrin complex are the micro-aggregates, based on inclusion complexes between methyl orange and cyclodextrins forms vesicle-like particles which have pH responsive properties.¹⁰³ Moreover, the first experimental therapeutic with cyclodextrins self-assemblies, was developed and applied in humans to provide targeted delivery of RNA (SiRN A).¹⁰⁴ In a similar manner, novel quaternary ammonium β cyclodextrin (QA β CD) nanoparticles were developed, as drug delivery carriers for doxorubicin (DOX), a hydrophobic anticancer drug, across the blood brain barrier. These nanoparticles enhance 2.2 times the permeability of DOX across the bovine brain microvessel endothelial monolayers.¹⁰⁵

A recent supramolecular nanoarchitecture and the concept of this type of nanoparticles, is very well shown by J. Huskens et al (2015).¹⁰⁶ This supramolecular nanoparticle was based on the hetero-ternary host-guest complexation between cucurbit [8]uril (CB[8]), methyl viologen (MV), and azobenzene (Azo), while using the monovalent, small-molecule, non-fouling Azo-carboxybetaine analog (Azo-Zwit) as the shell forming component. In this nanostructure, the importance of the supramolecular interactions with the pH changes on the nanoparticle stability is shown.

Insert Figure 7

Many developments have been done in this field in the last years, and there are many applications in drug delivery and nanoimaging in progress, not as many in molecular detection, though, or within the supramolecular analytical chemistry area. Then, new studies and developments are open in this field. For example, by specific small molecules interactions, chiral supramolecular nanoparticles were developed.¹⁰⁷ Supramolecular chirality at metal nanoparticle surfaces by cysteine and its derivatives was studied. Self-assembly layers of several ligands, namely L-cysteine, L-penicillamine and α -methyl-L-cysteine, on different silver nanoparticles were studied, by means of absorption and electronic circular dichroism spectroscopy in UV–vis range and surface enhanced Raman scattering spectroscopy.

2.5. Biodegradable Nanoparticles

In order to develop drug delivery systems, biodegradable Nanoparticles are developed based on the combination of polymer and supramolecular chemistry joined to Organic and Inorganic Nanoparticles. By this way it is possible to tune the flexibility of the polymeric chains and interaction between them to get Nanoparticles with different porosities, densities and functionalities. By this manner it is possible to design different types of nanoparticles, applied to bioanalytical chemistry, clinical chemistry, nanoimaging and nanomedicine. These materials should be biocompatible, and they are used for detection of biological events, nano-imaging, cell tracking, drug delivery, cancer treatments, etc. Polymeric nanoparticles, core-shell nanoparticles, and Nano supramolecular nanoparticles provide many possibilities to tune and optimize their targeted application.

Biodegradable nanoparticles made by monomers poly-lactic acid (PLA),¹⁰⁸ poly-glycolid acid (PGA), and co-polymers, formed by both monomers (PLGA)^{109, 110} are found in literature, and are the most biocompatible materials¹¹¹ for drug delivery as well as other applications, such as poly-lactic malic co-polymers (PLMA)¹¹² synthesised, applied as shells in nanostructures. For this reason, many researchers are studying the application of biodegradable nanoparticles for drug delivery. For example, preparation of PLGA nanoparticles, containing estrogen as drug model loaded for controlled delivery was synthesised,¹¹³ and these types of synthetic methods of drug loaded nanoparticles, can be applied to develop cancer detection and treatment, like the synthesis and characterisation of tamoxifen-loaded magnetite/poly (L-lactic acid) composite nanoparticles (TMCN), and its in vitro anti-cancer activity against MCF-7 breast cancer cells.¹¹⁴ Another example, it was targeting cancer cells, using PLGA nanoparticle surface, modified with monoclonal antibody.¹¹⁵ Moreover, studies of surface functionalization of PLGA nanoparticles, by heparin or chitosan conjugated pluronic on tumor targeting, were done in order to enhance tumor imaging and therapy.¹¹⁶ And, due to Photodynamic Therapy (PDT), a novel therapeutic method for the treatment of many tumors, zinc phthalocyanine loaded PLGA biodegradable nanoparticles for photodynamic therapy in tumor-bearing mice were designed.¹¹⁷ Tuning of the polymer chemical properties with polyethylene glycol (PEG) chains was used to modify these polymers, avoiding protein and peptide adsorption,^{118, 119} improvements in cellular uptake¹²⁰ and biodistribution,¹²¹ and controlled drug delivery.^{122, 123}

There are many other examples, from polymers to biodegradable nanoparticles,¹²⁴ membranes, films, etc., such as cyanoacrylate polyester polymers,¹²⁵ that did not show

the best biocompatibility in nanomedicine applications, compared to PLA, PLGA polymers absorbed through natural pathways¹²⁶ and approved by the FDA.¹¹³ Thus, with the recent applications of nanoscience in nanoscale materials and biomedical research, the importance of nanotoxicological studies are shown in recent publications.¹²⁷

The current interest to improve the still existing controlled drug delivery and new nanostructures is still developing. Supramolecular nanoparticles based on polymers and supramolecular systems, can be applied to drug delivery application as well as stimuli responsive multifunctional nanodevices.^{128, 129} Consequently, polymeric chains give flexible branches that can be chemically modified with macrocycles and by non-covalent interaction, form polymeric-supramolecular nanoparticles that encapsulate drugs of pharmaceutical interest. These drugs can be delivered, modifying the media. From the combination of hyperbranched poly (ethylene glycol)-based supramolecular nanoparticles, pH-sensitive properties were designed and used for targeted drug delivery. *Via* host–guest recognition between benzimidazole anchored poly (ethylene glycol)-hyperbranched polyglycerol (PEG-HPG-BM) and folic acid modified CD (FA-CD), supramolecular nanoparticles (SNs) were fabricated.¹³⁰ In neutral aqueous conditions, SNs could load the model drug DOX. While under intracellular acidic conditions, the loaded-drug would be released due to the protonation of BM. This protonation allows supramolecular nanoparticles to expand or even disassemble, which shows the pH-dependent property.

Supramolecular nanoparticles, based on polyacrylates, were functionalized with adamantane and β -cyclodextrin strong host–guest interactions self-assemble, to form supramolecular nanoparticles for tumor-targeted drug delivery. Folic acid was

incorporated into the nanostructure, in order to impart the targeting specificity towards selected cancerous cell lines. The *in vivo* drug delivery study, using DOX-loaded supramolecular nanoparticles was performed. Tumor-bearing nude mice were treated with DOX-loaded supramolecular nanoparticles, and the analysis results indicate DOX-loaded supramolecular nanoparticles have the capability to enhance the therapeutic effects of DOX for effectively inhibiting tumor growth.¹³¹ Similarly, new cavitands such as Water-Soluble Pillar[6]arenes, cargo DOX-Based Prodrug Supramolecular Nanoparticles for Self-Catalyzed Rapid Drug Release, were synthesized.¹³²

The relevance of chemistry nanoparticles surface modification not only referred to aggregation issues, like overcoming the use of PEG linkers in cellular media,¹³³ but also showed the enhanced effect that it could ideally have, compared with non modified nanoparticles. In this way, supramolecular nanoassembly with L- α -phosphatidylcholine and DSPE-PEG [1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)]] were developed, and the efficacy was further increased just by decorating the nanoparticle surface with tumor-homing peptides.¹³⁴

In addition to biocompatibility, targeted specificity, and enhanced drug delivery of these nanostructures new form of data analysis from nanoimaging, is in progress. As an example, we could mention a pretargeted Positron Emission Tomography Imaging that employs supramolecular nanoparticles with *in vivo* bioorthogonal chemistry.¹³⁵

In general, based on all these supramolecular concepts shown, it was not difficult to achieve the right sizes of nanoparticles, which is a very important parameter to control, depending on future applications¹³⁶. However, there are no exhaustive studies, considering the needs of applications in biological media. It should be noted, that

organized systems, such as polymeric vesicles, can be engineered in order to be used as targeted drug delivery systems and nanoimaging platforms as well.¹³⁷

2.6. Photonic Hybrid Supramolecular Nanostructures

This last part of the review shows the importance of the interdisciplinarity of different chemistry fields.

The challenge of the Photonics Nanomaterials developments, it is to tune the plasmonic properties depending of the application. From the interactions of Supramolecular systems, molecular spacers, and polymers adsorbed or covalent bonded with the metallic surface, can be modified the electronic properties in the near field.

Hybrid supramolecular nanostructures of organic and inorganic molecules have a promising potential in the enhancement of electronic and energy transduction for nanomedicine, nanosensors and technological applications.

Core-shell nanoparticles are designed in order to add different functionalities on their nanostructure, as fluorescent,¹³⁸ drug loaded,¹³⁹ magnetic,¹⁴⁰ and metallic,¹⁴¹ cores, while their shells can be used as fluorescent containers¹⁴² or cargo shells and surface to be chemically modified,¹⁴³ activated, bioconjugated¹⁴⁴ for tracking applications and drug delivery,¹⁴⁵ to add to the whole nanostructure a final specific targeted application. Magnetic core-shell nanoparticles were applied to magnetic resonance imaging,¹⁴⁶ targeting cells¹⁴⁷ and drug delivery applications for cancer treatments.¹⁴⁸

Insert Figure 8

Another similar design concept is the development of nanoparticles, based on a metallic core, modified by molecular spacer as, for example, gold nanoparticles containing multiple long, flexible linkers, decorated with lactose, β -cyclodextrin for site specific drug delivery systems.¹⁴⁹ As an example of the tuning of material properties, from the combination of supramolecular chemistry like Cyclodextrins, conductive nanomaterials like graphene, and metallic nanoparticles like gold ones, it was possible to develop strong supramolecular capability for electrochemical thrombin aptasensor by Guo et al.¹⁵⁰

The importance of surface chemistry in nanoparticles is not shown only in the molecular recognition field in nanodevices; with the huge nanomaterial developments, it is necessary, in many cases, to modify the surface chemistry to avoid their possible toxicological problems in cells. It is known that core-shell nanoparticles as QDs are toxic,¹⁵¹ and coating their surface could modify their effect. CdSe QDs toxicological effect was diminished with (poly-ethylene glycol) PEG coated surfaces on Caco-2 cells.¹⁵²

The inclusion of metallic nanoparticles into polymeric nanoparticles and supramolecular nanoparticles, add the intrinsic properties of each component in order to design the nanoarchitecture wanted. Therefore, it could improve final properties, combining and tuning them. In this way, self-assembled gold nanoclusters for Bright Fluorescence Imaging and Enhanced Drug Delivery were developed, combining plasmonic and polymeric properties, only modifying the pH of the medium.¹⁵³

Insert Figure 9

Another example of nanoarchitecture tuning for versatile application was shown by Boudreau et al., where FRET Enhancement in Multilayer Core–Shell Nanoparticles¹⁵⁴ was developed. This proof of concept was applied in a first step for a non specific molecular recognition. The nanoarchitecture was based on a silver core, modified with fluorescent energy acceptor silica shell and a cationic polythiophene polymer as fluorescent donor, adsorbed over the nanoparticle surface by electrostatic interactions; allowing the short polythiophene polymeric chains enhanced detection via a FRET pathway coupled to metal enhanced fluorescence (MEF).¹⁵⁵ After that, a DNA sensing nanoarchitecture was designed, combining the molecular recognition capabilities of the cationic conjugated polymer as signal transducer of the double strand DNA specific interaction event, over a highly fluorescent bioconjugated core-shell nanoparticle, for an ultrasensitive unamplified DNA detection.¹⁵⁶ This biophotonic nanoarchitecture was applied to the rapid and simple genotyping of blood group antigens from unamplified genomic DNA measured using standard flow cytometers. This PCR-free approach could be applied to any known genetic polymorphism.¹⁵⁷

Insert Figure 10

Finally, it is important to mention that a new field within the nanomedicine is developing, such as supramolecular diagnostics and nanomedicine, opening different studies related to synthesis, characterisation, applications, and toxicity evaluations, which will allow development of new methods of diagnostics and therapies. A proof of concept was developed recently by Bracamonte et al. about a Switch on/off enhanced

fluorescence control for detection and molecular release, using a simple chemistry reaction based on nanosupramolecular architecture.¹⁵⁸

3. Future Perspectives

The future perspectives should be discussed from different points of view and at a chemical level, for the different applications of this review. From supramolecular systems, based on non covalent interactions as antigen-antibodies, specific recognition and bioconjugation techniques, based on organic chemical reaction, joined to the knowledge of Molecular Biology, it is possible to get targeted biomolecular recognitions, controlled molecular linking over nano-platform surfaces. These nano-platforms could be based on inorganic and organic materials, combining different properties. Developments of new nanostructures will be applied for research in different fields of high impact in Nanoscience and Nanotechnology as new Nanomaterials, Nanophotonics, Biophotonics, Nanoimaging, Nanofluidics and Nanomedicine. From these different fields, developments promising new tools will be available for different areas of science, such as Biology and Medicine. Nanoimaging for biomedical imaging applications, Diagnostics with Ultrasensitive detection, Optical Biosensors, Fiber Optics Biosensors; Drug Delivery Systems for new and specific targeted clinical therapies and more. The future perspectives of all these developments come from multidisciplinary fields, especially from advanced new nanomaterials with particular electronic and plasmonic properties.

The electronic conduction is very important for signal transductions. In the last years, many developments of plasmonics were done for the next generation, integrating circuitry based on coupling between surface plasmon polaritons and nanostructures in the

near-field¹⁵⁹. Moreover, new supramolecular assemblies with intrinsic electronic properties showed to be applied as supramolecular nanowires for optoelectronic devices¹⁶⁰.

New materials are currently being developed from the combination of organic chemistry and plasmonics, for many applications. The surface modification of infrared metallic nanoparticles by conductive polymers gives as result Plasmonic Nanoantennas, which are able to photogenerate charge carriers¹⁶¹. These new materials developed with particular electronic properties can be applied for signal enhancement and signal amplification for biochips, and Lab on-chip applications¹⁶². As an interesting example, we could mention the individual bacteria detection based on the bacteria interaction with the gap of two gold nanorods with two-photon-induced luminescence (TPL) measurements by optical trapping¹⁶³.

Other examples of multidisciplinary developments in Nanomedicine, joining the knowledge of microbiology and supramolecular chemistry are the tuned, organized systems as nanorobots formed by Magneto-aerotactic bacteria and nanoliposomes for controlled drug delivery on tumour hypoxic regions¹⁶⁴.

In all the advance trends, when a combination of properties for a specific target was needed like specificity, signal amplification, signal transduction for detection or tracking, it was necessary to tune the different parts of the whole nanostructure. There are examples of colloidal dispersions, as core shell nanoparticles, where their Luminescent properties were tuned for optimal enhancements and detection of molecular events via MEF and FRET mechanisms, incorporating, by covalent and no-covalent interactions, fluorophores, polymers, and DNA over their nanostructure¹⁶⁵.

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Figures

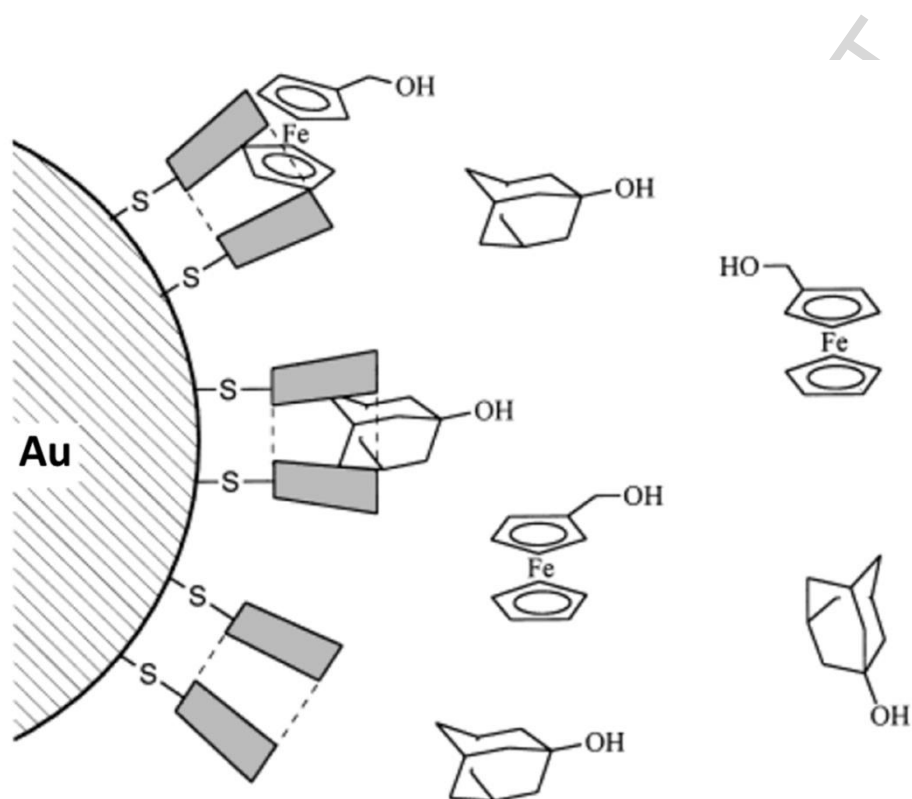


Figure 1. Competitive binding of ferrocenemethanol and 1-adamantanol to the CD Hosts immobilized on gold nanoparticles. Reprinted with permission from Ref 22 (Kaifer group). Copyright 2000 Am. Chem. Soc.

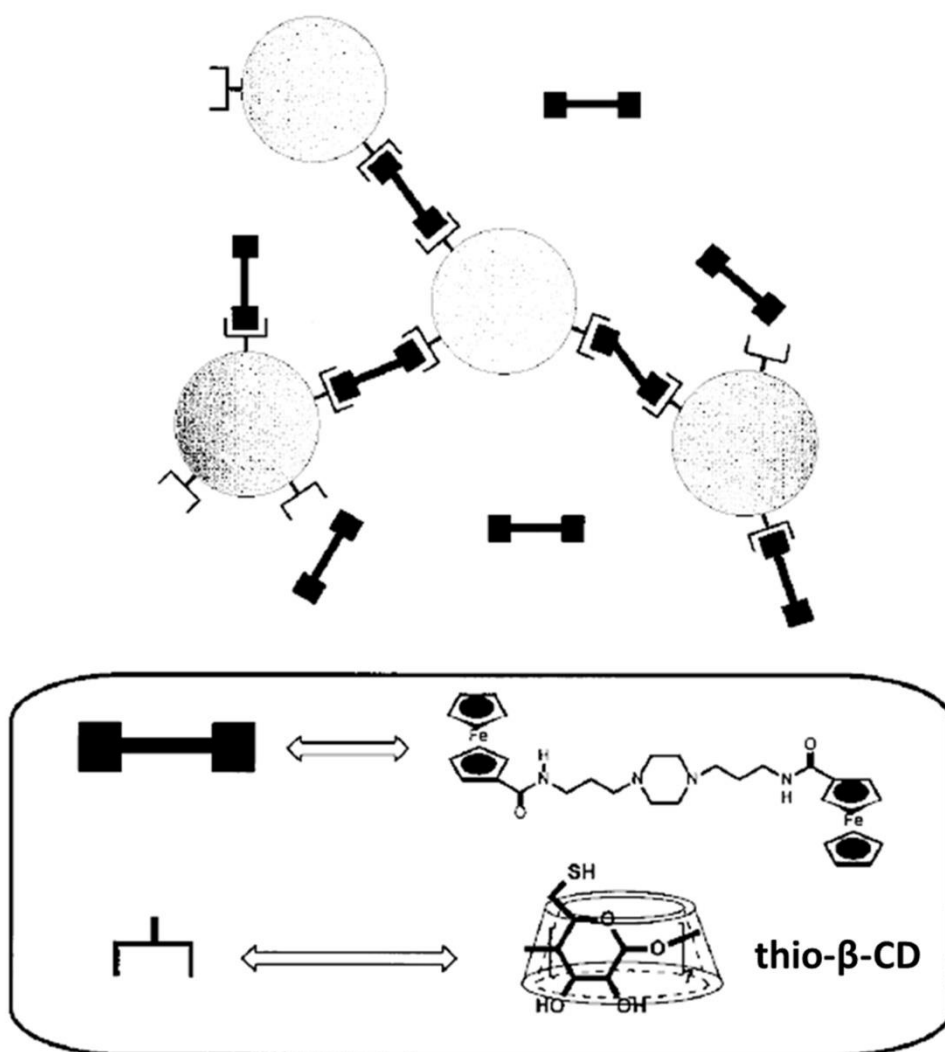


Figure 2. Cyclodextrins gold nanoparticles grafted. Reprinted with permission from Ref 37 (Kaifer group). Copyright 1999 Am. Chem. Soc.

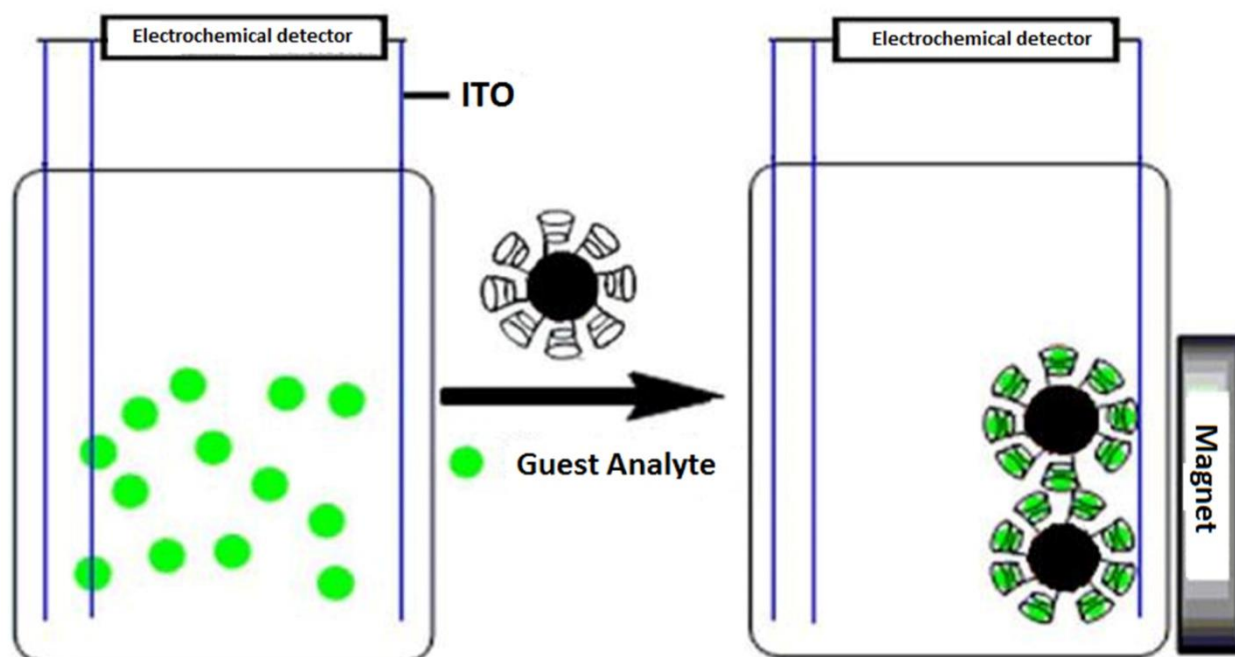


Figure 3. Schematic illustration of magnet controlled electrochemical detection of dopamine. Reprinted with permission from Ref 63 (Peng et al. group). Copyright 2009 Springer.

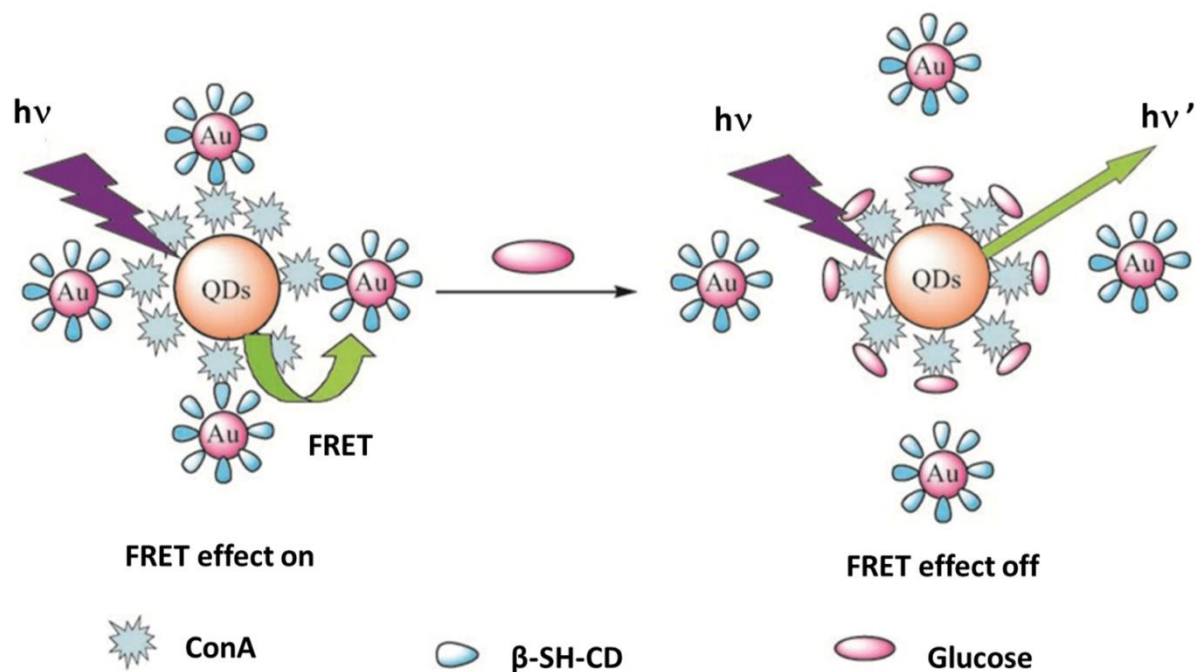


Figure 4. Chemical structure of the QDs-Concanavalin A-Au-CDs-AuNPs nanobiosensor and schematic illustration of its FRET-based operating principles (It is known that concanavalin A is a lectin protein that can bind glucose). Reprinted with permission from Ref 90 (Yu et al. group). Copyright 2008 Wiley-VCH.

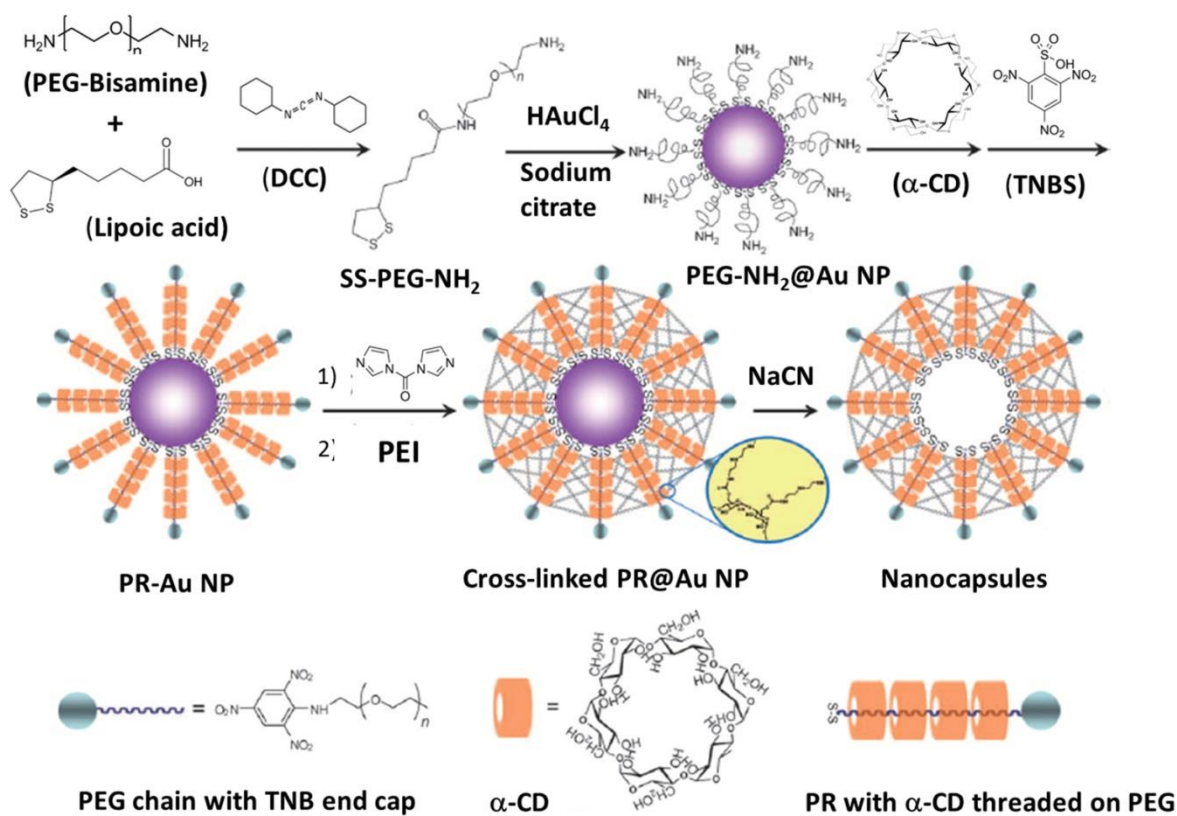


Figure 5. Synthesis of the supramolecular nanocapsules, including illustrations of structures of the nanocapsules and precursors. Reprinted with permission from Ref 101 (Li et al. group). Copyright 2009 Wiley-VCH.

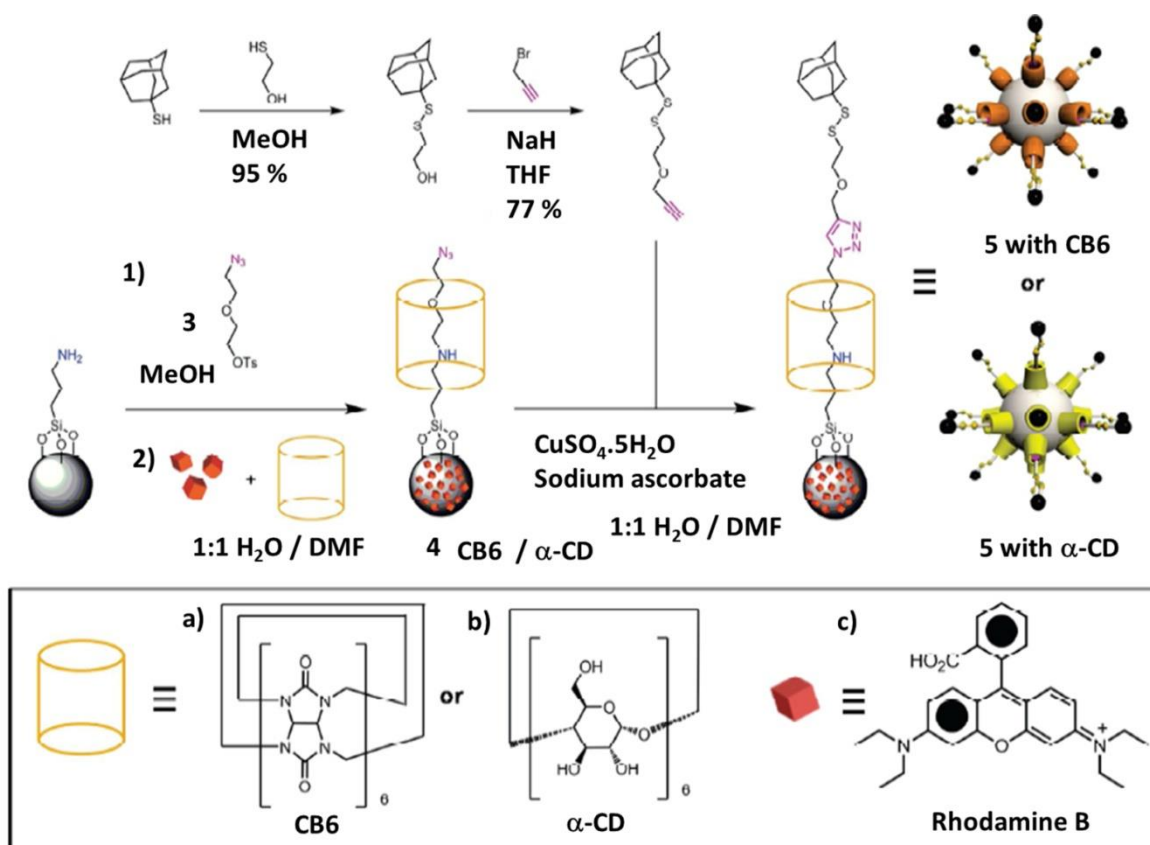


Figure 6. Synthesis of the Alkyne-Terminated Stopper and Assembly of Disulfide Based Snap-Top Nanocarriers. Mesoporous silica nanoparticles as delivery vehicle, cyclodextrins or cucurbiturils as capping agent, and Rhodamine B as cargo. Reprinted with permission from Ref 102 (Stoddart et al. group). Copyright 2010 ACS.

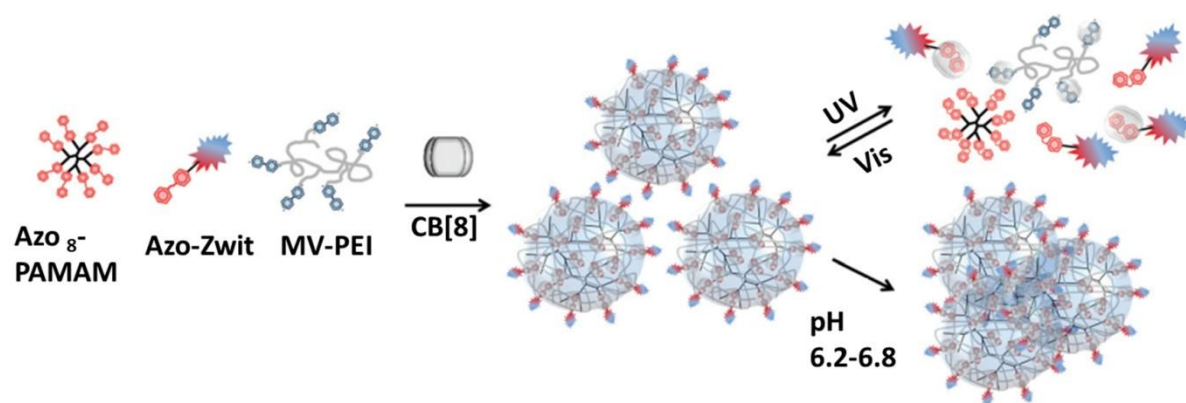


Figure 7. Zwitterionic supramolecular nanoparticles: self-assembly and responsive properties. Reprinted with permission from Ref 106 (J. Huskens et al. group). Copyright 2015 RSC.

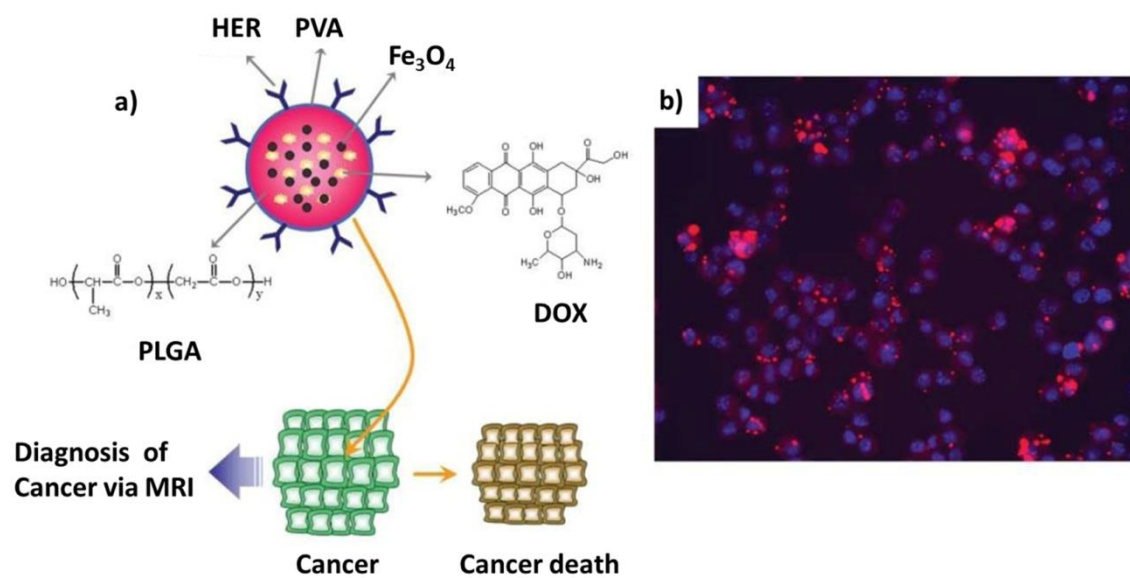


Figure 8. a) Schematic illustration of magnetic PLGA nanoparticles for diagnosis and treatment of cancer. b) Fluorescence microscopy image of cells incubated with PLGA Nanoparticles. Reprinted with permission from Ref 148 (Haam et al. group). Copyright 2007 RSC.

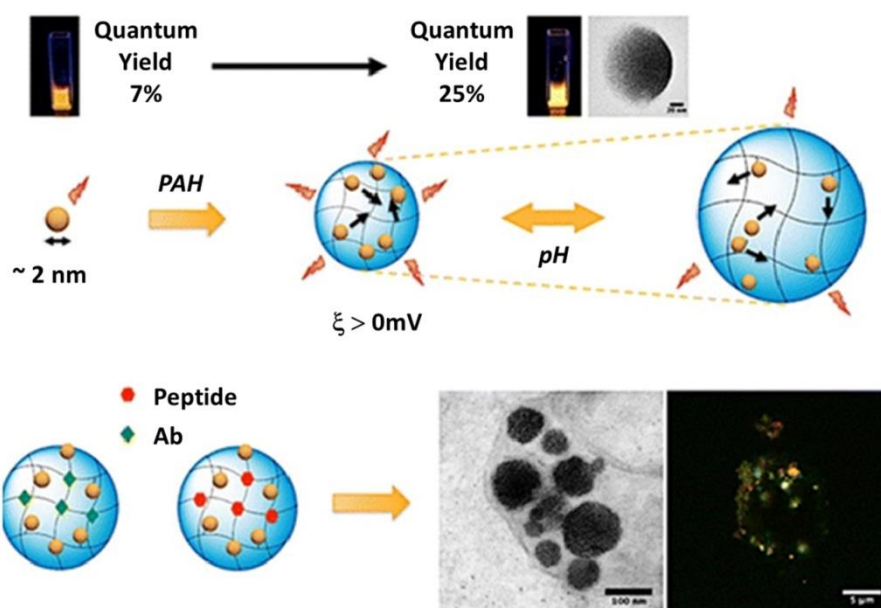


Figure 9. Schematic illustration of Supramolecular Nanoparticles applied for Nanoimaging and Drug delivery application. Reprinted with permission from Ref 153 (Niko Hildebrandt and Xavier Le Guével et al. group). Copyright 2016 ACS.

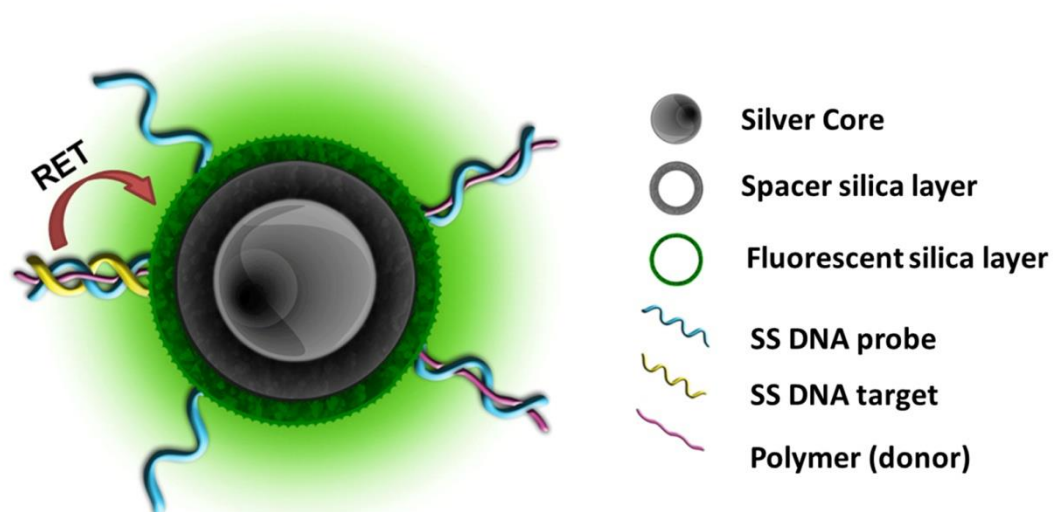


Figure 10. Fluorescent multilayer core-shell NPs architecture for DNA detection in three steps. 1) target-ready NPs are prepared by complexing ssDNA probe-grafted NPs with a fluorescent polymer transducer; 2) hybridization of target DNA with ssDNA probes activates the polymer transducer as energy donor toward dye-doped silica shell and excitation at 410 nm generates fluorescence emission by acceptor molecules at 550 nm. . Reprinted with permission from Ref 156 (Denis Boudreau et al.). Copyright 2011 ACS.

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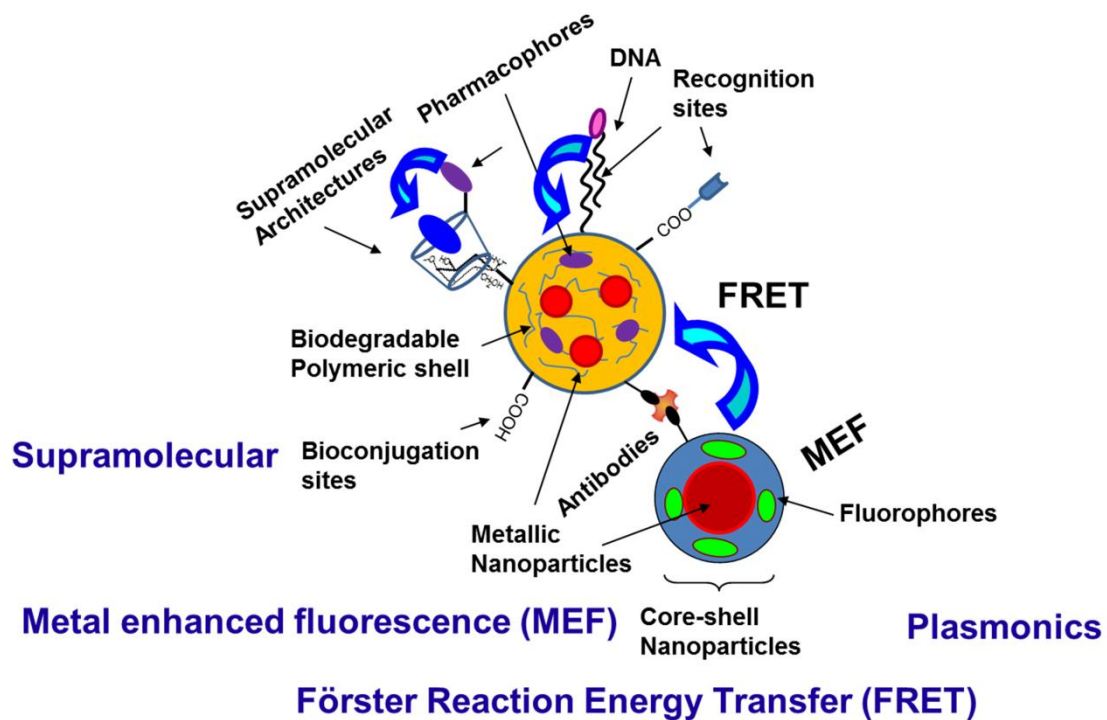
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ACCEPTED MANUSCRIPT

Graphical Abstract

Multifunctional Nanostructures

Research highlights

- Design of New Smart Nanostructures applied to Nanosensors and Drug delivery systems.
- Nanoparticles based on Supramolecular Chemistry.
- Photonic Hybrid Nanomaterials.
- Enhanced Signals based on Supramolecular interactions, plasmonic effects and energy transfer processes applied to molecular and biological structures tracking for detection diagnostics and developments in Nanomedicine.