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Nanoparticles for Detection and Diagnosis

Sarit S. Agasti, **Subinoy Rana**, **Myoung-Hwan Park**, **Chae Kyu Kim**, **Chang-Cheng You**, and **Vincent M. Rotello***
Department of Chemistry, University of Massachusetts, 710 North Pleasant Street, Amherst, MA, 01003 (USA)

Abstract

Nanoparticle-based platforms for identification of chemical and biological agents offer substantial benefits to biomedical and environmental science. These platforms benefit from the availability of a wide variety of core materials as well as the unique physical and chemical properties of these nanoscale materials. This review surveys some of the emerging approaches in the field of nanoparticle based detection systems, highlighting the nanoparticle based screening methods for metal ions, proteins, nucleic acids, and biologically relevant small molecules.

Keywords

Nanoparticles; assembly; absorbance; surface plasmon band; fluorescence; protein; DNA; bacteria

1. Introduction

Detection of chemical and biological agents plays a pivotal role in medical, forensic, agricultural, and environmental sciences [1]. Sensitive methods that allow identification of biomarkers such as proteins and nucleic acids at early disease states provide the prospect of better health and more effective therapy. Technological platforms that provide sensors of high sensitivity, selectivity and stability are therefore in high demand.

Sensing systems consist of two functional components: recognition elements for binding with target analytes and a transduction process to signal the binding event. The efficiency of these two components are critically related to the outcome of the detection process in terms of the response time, signal-to-noise (S/N) characteristics, sensitivity, and selectivity of the system. Thus, the challenges in development of novel detection systems have been concerned with improving the recognition process as well as designing new signal transduction mechanisms. Nanomaterials provide novel systems for the pursuit of new recognition and transduction processes, as well as increasing the signal-to-noise ratio through miniaturization of the system components [2].

Nanoparticles (NPs) possess several distinctive physical and chemical attributes that make them promising synthetic scaffold for the creation of novel chemical and biological detection systems [3]. Indeed, in the last few years nanostructured materials, such as noble metal

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Tel: (+1) 413-545-2058 Fax: (+1) 413-545-4490 rotello@chem.umass.edu.

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nanoparticles, quantum dots, and magnetic nanoparticles, have been employed in a broad spectrum of highly innovative approaches for assays of metal ions, small molecules and protein and nucleic acid biomarkers [4,5,6,7]. In addition to the large surface-to-volume ratio that favors miniaturization, nanoparticles possess unique optical, electronic and magnetic properties depending on their core materials. Furthermore these properties of the nanomaterials depend on their size and shape, and vary with their surrounding chemical environment. Additionally, nanoparticles can be fashioned with a wide range of small organic ligands and large biomacromolecules by using tools and techniques of surface modification. Each of these capabilities has allowed researchers to design novel diagnostic systems that offer significant advantages in terms of sensitivity, selectivity, reliability and practicality. This review provides recent research advances involving the use of nanoparticles in the detection and diagnosis of analytes including metal ions, small molecules, nucleic acids, proteins, and microorganisms.

2. Optical Detection of Metal Ions and Small Molecules

2.1. Fluorescence-Based Detection Using Nanoparticles

Quantum dots (QDs) are characterized by several unique intrinsic optical properties [8]. The properties include broad absorption spectra with high extinction coefficient, along with a narrow emission with a full width at half maximum (FWHM) of 20-30 nm. The QD emission can also be readily tuned by changing the nanocrystal size, and is environmentally responsive. These intrinsic optical properties of QDs make them promising candidates for optical detection of various analytes. For example, detection of cyanide was achieved using 2-mercaptoethane sulfonate functionalized CdSe nanoparticles by monitoring the quenching of QD emission upon addition of CN^- [9]. Quenching of QD emission was observed in the presence of CN^- ions leading to a detection of μM concentration of CN^-. Importantly, the presence of SO_4^{2-}, NO^{3-}, Cl^-, Br^- and acetate anions in the system did induce any quenching of QD emission In another example, acetylcholine (ACh) was used to quench the emission of calix[4]arene coated CdSe/ZnS QDs [10].

The efficiency of QDs as donors in FRET processes has been exploited in sensing of local pH, metal ions and small molecules. For pH sensing Snee and coworkers have utilized a conjugated system comprising of a pH-sensitive squaraine dye and QD [11]. The dye absorbance depends on the solution pH, correspondingly the FRET efficiency also become a function of environmental pH. Similarly, detecting system targeting the explosive 2,4,6-trinitrotoluene (TNT) was developed by Mattoussi *et al.* [12]. The QD was functionalized with a recognition element (single chain antibody fragment specifically selected against TNT). Preassembling a TNT analog, consisting of a dark quenching dye with the antibody binding site quenches the QD emission through FRET. When the assembly was exposed to TNT, it displaces the quencher, disrupting the energy transfer from the QDs to the quencher and recovering the QD emission.

Gold nanoparticles (AuNPs) have extraordinarily high molar extinction coefficients (1×10^9 M^{-1} cm^{-1} for d = 20 nm AuNP) as compared to common organic dyes (10^4-10^6 M^{-1} cm^{-1}) [13,14]. Therefore, AuNPs can be treated as nonmolecular chromophores with excellent light collecting ability. Their exceptional quenching ability makes them suitable energy acceptors in the FRET based assays [15]. In one example, anionic tiopronin-coated AuNPs were used to efficiently quench the fluorescence of Poly-pyridyl complex $[Ru(bpy)_3]^{2+}$[16]. The fluorophore then can be dissociated from the nanoparticle surface by addition of electrolytes such as K^+, Bu_4N^+, and Ca^{2+} salts. Similarly, selective detection of aminothiols was possible by the use of Nile red-adsorbed AuNPs [17]. Zhu, Li and collaborators have devised a Cu^{2+} sensor by employing bispyridyl perylene bridged AuNPs, where the initially quenched fluorescence of perylene is recovered by Cu^{2+} ions through formation of stronger pyridine-Cu^{2+} coordination [18]. Recently, a phosphorescent sensor for alkaline earth metal ions and

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transition metal ions have been devised based on lanthanum complexes of bipyridine-functionalized AuNPs [19].

2.2. Colorimetric Detection

A promising avenue for analyte detection arises from the unique size and shape dependent optical, magnetic and electronic properties of nanomaterials. For instance, spherical gold nanoparticles (AuNPs) exhibit a variety of colors in solution from brown to violet as the core size increases from 1 to 100 nm. Spherical AuNPs usually exhibit an intense absorption peak from 500 to 550 nm, corresponding to the surface plasmon band of nanometer scale noble metal nanoparticles [20]. This absorption arises from the collective oscillation of the valence electrons due to resonant excitation by the incident photons. Surface plasmon resonance (SPR) is absent in both small nanoparticles ($d < 2$ nm) and bulk materials and strongly reliant on the particle size. Not only to the nanoparticle size, the SPR is also sensitive to the surrounding environment such as ligand, solvent and temperature and most importantly SPR is strongly dependent on the proximity to other nanoparticles. Thus, clustering of AuNPs of appropriate sizes ($d > 3.5$ nm) evokes interparticle surface plasmon coupling, resulting in a significant red-to-blue shifting (to ca. 650 nm) and broadening of the SPR band that can be readily observed by the naked eye at nanomolar concentrations [21].

The colorimetric detection of alkali metal ions using NPs was achieved by the incorporation of chelating agents onto the gold nanoparticle surface. AuNPs were functionalized with 15-crown-5 moieties to detect the physiologically important potassium ions. The presence of K^+ induces the aggregation of 15-crown-5 functionalized 18 nm AuNPs through the sandwich complex formation which results in a red-to-blue color change at μM to mM concentration of K^+ [22]. This system has been extended by incorporating 12-crown-4 onto the AuNPs surface to detect sodium ions [23]. Likewise, phenanthroline-functionalized 4 nm AuNPs to detect Li^+ and lactose-functionalized 16 nm AuNPs have been used to sense Ca^{2+} have also been constructed [24,25].

Heavy metal ions such as Pb^{2+}, Cd^{2+}, and Hg^{2+} are quite toxic, making their detection of great importance for environmental science. Hupp *et al*. have reported a simple heavy metal ion sensing system based on the aggregation of nanoparticles functionalized with appropriately designed ligands where the surface carboxylates act as chelating groups and the nanoparticle bridging is driven by heavy-metal ion chelation by Pb^{2+}, Cd^{2+}, or Hg^{2+} (≥400 μM) [26,27]. A colorimetric sensor for Pb^{2+} was also developed by forming mixed monolayer-protected AuNPs carrying both carboxylate and 15-crown-5 functionalities [28]. In this system aggregates of AuNPs form due to hydrogen bonding interaction between carboxylic acid residues, and Pb^{2+} ions disrupt the hydrogen-bonded assembly by associating with crown ether moiety and generating an electrostatic repulsion between the AuNPs, resulting in. a blue to red color change. Similarly, AuNPs have been fabricated with cysteine and peptide-functionality to detect Cu^{2+} and Hg^{2+}, respectively [29,30]. Recently, DNA-functionalized AuNPs have been employed for the detection of Hg^{2+} by Mirkin *et.al.* using thymidine- Hg^{2+}-thymidine coordination chemistry [31].

In ionic sensing, simultaneous addressing of selectivity and sensitivity issues are the key goals. Liu and Lu have provided an elegant example of selective and sensitive colorimetric Pb^{+2} biosensors implementing DNAzyme-directed assembly of AuNPs [32,33,34,35,36]. Initially the DNAzyme provides blue-colored assemblies of the DNA-functionalized AuNPs through Watson-Crick base pairing. The presence of Pb^{2+} in system activates the DNAzyme, which subsequently cleaves the substrate strand to dissemble the AuNPs resulting in a blue-to-red color change.

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In anion sensing, Kubo et al. have reported a colorimetric sensing of oxoanions such as AcO^{-}, HPO_4^{2-}, and malonate in aqueous methanol solution by using isothiouronium group functionalized AuNPs [37]. Similarly, thioglucose-grafted AuNPs have been fabricated to sense fluoride anions in water [38].

In neutral molecule sensing, Geddes *et al.* have demonstrated glucose sensing by using assemblies of concanavalin A (Con A) and high-molecular-weight dextran-coated AuNPs on the basis of a competitive colorimetric assay [39,40]. Con A is a multivalent protein having four sugar binding sites at pH 7. Due to its multiple binding sites, it allows dextran-coated nanoparticles to assemble around its binding sites. This assembly affords cross-linked nanoparticles with broadened and red-shifted SPR of AuNPs. The presence of glucose in the system releases the individual dextran-coated AuNPs by competitively interacting with Con A, generating a blue-to-red shift with a dynamic sensing range of 1 – 40 mM. The incorporation of MUA-AuNPs into the polymer matrix of molecularly imprinted polymers (MIPs) has been used to provide colorimetric sensor for adrenaline [41]. The initially shrunken MIP gel placed between two glass slides in the absence of adrenaline affords the close proximity of AuNPs. However, selective rebinding of the target analytes with the MIP causes swelling of the MPI gel. This swelling process results in separation of the nanoparticles with a blue-shift in the SPR band of the immobilized AuNPs.

Aptamers are single-stranded oligonucleic acid-based binding molecules that can bind to a variety of targets with high affinity and specificity. An effective cocaine sensor was designed by Lu and coworkers, allowing quantification in the range of 50 to 500 μM [42,43,44].

3. Nanoparticle-Based Detection of Proteins

3.1. Fluorescence-Based Detection Using Nanoparticles

The identification of proteins offers direct applications in therapeutics, forensic analysis and environmental monitoring. QDs have shown potential for the detection of proteins. Nagasaki e*t al.* reported a biotin-PEG/polyamine CdS quantum dot [45]. Due to the specific interaction of this QD with Texas Red-labeled streptavidin, an effective fluorescent energy transfer (FRET) takes place which is proportional to the concentration of the dye-labeled protein. It can thus be applied as a highly sensitive detection motif. In another system, Kim *et al* fabricated a FRET donor-acceptor couple using biotinylated AuNPs and streptavidin coated QDs [46]. In presence of avidin, the fluorescence of QDs is regenerated due to the interruption of streptavidin-biotin interaction (Fig. 7). The same concept was also used to detect glycoproteins [47].

Luminiscent QD bioconjugates were applied in detecting the proteolytic activity of several enzymes by Mattoussi [48]. For this study, dyes labeled multifunctional modular peptides containing a substrate sequence were designed. The peptides were then self-assembled on dihydrolipoic acid-capped QD surface to get an efficient FRET from the QD to the proximal dye. Presence of proteases in the system cleaves the substrate strand, altering the FRET signature.

Another paradigm for detection of proteins by functionalized gold nanoparticles was introduced by Rotello and co-workers employing “chemical nose approach” [49]. This approach relies on array-based sensing using selective recognition elements. They fabricated a sensor array by using cationic AuNPs with various head groups and anionic poly(p-phenyleneethynylene) (PPE) fluorescent polymer that serves as the fluorescence transduction element. In this sensor design, the cationic nanoparticles significantly quench the intrinsic fluorescence of the PPE polymer. Competitive binding of analyte proteins releases the PPE

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polymer, resulting in a fluorescence recovery (Fig. 9). Linear discrimination analysis (LDA) was then used to identify unknowns from the training set.

3.2. Colorimetric Detection

AuNPs with diverse ligand functionalities provide one of the potential scaffolds in detecting proteins. For example, the aggregation induced by specific recognition of galactosefunctionalized AuNPs with agglutinin, a bivalent lectin, causes a visible color change that can serve as the colorimetric sensor for proteins [50].Other glyconanoparticles have also been used for detecting and quantifying several proteins such as Concanavalin A [51] and cholera toxin [52] by colorimetric detection methods.

The optical properties of the metallic NPs have been employed in amplifying the detection of proteins. Willner and coworkers have amplified the detection of aptamer-thrombin complexes in solution and glass surface as a result of catalytic enlargement of aptamer functionalized AuNPs [53]. The aptamer covalently attached to the glass surface binds first to the thrombin target. Then the aptamer-functionalized AuNPs was associated with the other thrombin binding site leading to a sandwich complex. The immobilized AuNPs are further enlarged in a growth solution containing $HAuCl_4$, CTAB, and NADH, which enhances the surface plasmon coupling interaction of adjacent nanoparticles [54].

The specific interaction of antigen-coated nanoparticle and the antibodies provide another avenue for detection of proteins. Rosenzweig and co-worker developed an immunoassay procedure in which AuNPs coated with protein A were used to determine the level of anti-protein A in aqueous and serum solutions [55]. The presence of anti-protein A causes aggregation of the antigen coated nanoparticle resulting in a change in absorption at 620 nm and thus can be sensed in the solution.

3.3. Bio-bar-code Assay

Mirkin's group has developed an AuNP-based bio-barcode assay to amplify the target analytes. This method provides highly multiplexed and ultrasensitive detection of proteins [56,57]. The bio-barcode assay was first employed to analyze PSA, which is a biomarker protein for prostate and breast cancer [58]. The recognition element for protein is monoclonal antibody functionalized on magnetic microparticle. The other component is an AuNP coated with both polyclonal antibodies for the target protein and oligonucleotides hybridized to bar-code strands. In this method, the magnetic microparticles first bind to the target protein followed by sandwich structure formation with AuNPs. A magnetic field is then applied to separate the complexed target from the sample solution and the bar-codes were released in buffer chemically or by heating. The barcodes were identified with attomolar detection limit using chip-based sandwich hybridization with ss-DNA functionalized AuNP probes followed by silver amplification method. This approach was also applied to multiplexed detection of protein using different biobar-coded AuNP probes [57].

4. Detection of Nucleic Acids

4.1. Fluorescence-Based Detection Using Nanoparticles

As with organic fluorescent dyes, the emission of semiconductor QDs can be effectively quenched by AuNPs in appropriate vicinity. Melvin *et al.* have designed a fluorescent competitive assay for DNA detection by using QDs and AuNPs as the FRET donor-acceptor couple [59]. In their protocol, the CdSe QDs linked to a short DNA strand are hybridized with a complementary DNA strand linked to an AuNP, leading to quenched assemblies due to the surface-contact between QDs and AuNPs. When unlabelled complementary oligonucleotides are present, the AuNP-DNA is displaced from the QD-DNA, regenerating the QD fluorescence.

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Nie and coworkers have developed a strategy for multiplexed DNA detection [60]. For this protocol, they labeled the target DNA with a fluorophore. Correspondingly, oligonucleotidefunctionalized polymeric microbeads were imbedded with QDs which are designed to emit at various specified wavelengths (other than target DNA). As shown in Fig. 11, microbeads with different ratios of QDs showed different emission intensities at different wavelengths. After binding with target DNA, single-bead spectroscopy was used to determine the presence and the identity of the target DNA. Later, Alivisatos and co-workers reported a DNA-QD conjugate, applicable to chip based DNA microarray for single-nucleotide polymorphism and multimarker detections [61]. These chip-based assays exhibited true-to-false signal ratios above 10 and the detection limit as low as 2 nM concentration of DNA-NP probes.

Tan's group developed highly fluorescent bioconjugated silica NPs as labels for chip-based sandwich DNA assays [62]. The silica NPs encapsulates large numbers of fluorophores inside a single NP which produces a strong fluorescence signal associated with each target recognition event without any preamplification. Moreover, the silica matrix provides a high photostability because of shielding effect to protect the fluorophores from environmental oxygen. The ultrasensitive DNA analysis assay showed a 0.8 fM detection limit using a bioconjugated NP-based sandwich assay and provided 100:7 discrimination between target DNA and one-base mismatched DNA sequences. They also utilized this bioconjugated NP-based bioassay for detection of pathogenic bacteria based on antibody-antigen interaction and recognition.

4.2. Colorimetric detection

The potential of NPs as DNA detection agents was first described by Mirkin *et al.* using oligonucleotide-functionalized AuNPs and sequence-specific particle assembly events induced by target DNA [63,64]. Since then, oligonucleotide-directed NP aggregation has been extensively used in the colorimetric detection of oligonucleotides [65,66,67,68,69,70]. Generally, two ssDNA-modified NPs are used for the detection of oligonucleotides. The base sequences in ssDNA are complementary to both ends of the target oligonucleotides. As illustrated in Fig. 13a, the presence of target oligonucleotide causes the NP aggregation. Concomitantly a change in optical properties of the NPs was observed. Intense absorptivity of NPs as well as strong and highly specific base-pairing of DNA molecules facilitates the ultrasensitive optical detection of oligonuceotides. Generally, when large AuNPs (e.g. 50 nm or 100 nm) were employed a better sensitivity in detection was achieved. Interestingly, based on simple electrostatic interaction such as single-base-pair mismatches, citrate-stabilized AuNPs were able to distinguish ssDNA and dsDNA at the level of 100 fmol [71].

Another advantage offered by the colorimetric technique for DNA detection is the tunable selectivity due to the sharp melting transitions of NP-labeled DNA assemblies. This advantage was utilized in a chip-based system based on a sandwich assay [72]. This assay consists of an oligonucleotide-modified glass slide, a NP probe and target DNA, as illustrated in Fig. 13b. The immobilized DNA strand recognizes the DNA of interest and changes the melting profiles of the targets from an array substrate. This change gave the differentiation of an oligonucleotide sequence from targets with single nucleotide mismatches with a high selectivity.

4.3. SERS-Based Detection

SERS using AuNPs has been used to sense DNA. Mirkin *et al*. used AuNP probes labeled with Raman-active dyes and oligonucleotides to accomplish multiplexed detection of oligonucleotide targets [73]. Using a sandwich assay and silver enhancement, SERS signals were observed from the immobilized Raman dyes. This method was able to discriminate between single nucleotide polymorphisms in six different viruses. Raman tags have also been incorporated into DNAfunctionalized AuNPs for the detection of DNA using SERS [74].

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4.4. Electrical and electrochemical detection

Electrochemical detection provides an alternative to optical approaches for the detection of DNA[75]. Using this strategy, DNA recognition events are transduced into electrical signals using NP mediators. Mirkin *et al*. have developed a DNA array detection method where the binding of oligonucleotide-functionalized AuNPs generates conductivity changes [76]. In their studies, target DNA has been detected at concentrations of 500 fmol with a point mutation selectivity factor of ~ 100,000:1.

The redox properties of NPs make them useful as electrochemical labels for the detection of oligonucleotides. Ozsoz *et al*. have shown that the incubation of a DNA-modified electrode with complementary DNA strands conjugated to NPs generated a gold oxide wave at +1.2 V [77]. A number of amplification strategies have been developed, including silver deposition [78] and the conjugation of electrochemically active groups onto NPs [79,80]. In one approach ferrocene-capped AuNP/streptavidin conjugates were attached to a DNA detection probe of a "sandwich" DNA complex on the electrode. [78,81]. Fan *et al*. likewise described a detection approach employing hybridization with AuNP-labeled reporter probe DNA and the subsequent treatment with $[Ru(NH_3)_6]^{3+}$ complexes [82].In recent studies, Willner *et al.* reported the electrochemical detection of DNA using aggregation of AuNPs on electrodes coupled with intercalation of methylene blue into the DNA [83].The methylene blue dyes act as electrochemical indicator for the formation of double-stranded DNA and the AuNP assemblies facilitate the electrical contact of methylene blue.

4.5. QCM-based Detection and Bio-Bar-Code Assay

Quartz crystal microbalances (QCM), are piezoelectric devices that provide an ultrasensitive mass sensor. QCM based technique of DNA sensing have been widely used in biodiagnosis, due to the high sensitivity, economic effectiveness, and convenient operation of QCM instruments [84]. In practice, immobilization of thiol-terminated ssDNA onto the gold coated QCM followed by a hybridization step with target oligonucleotides leads to a detectable signal. As a consequence of large surface to volume ratio of AuNPs, the introduction of a layer of AuNPs between the gold film and the immobilized ssDNA significantly improves the detection capacity of the system [85]. In an alternative way, "sandwich" approaches can also drastically improve the detection limit of the system [86,87,88,89,90]. In the "sandwich" approach one end of target oligonucleotides hybridizes with the immobilized ssDNA molecules (recognition elements) while the other end hybridizes with ssDNA-modified AuNPs (signal amplifier). To further improve the sensitivity of the QCM approach, catalyzed deposition of gold onto the amplifier AuNPs has also been demonstrated [91], with a detection limit of ~1 fM

The principle of bio-bar-code amplification described for protein analyes, has been employed for DNA detection [92,93]. As illustrated in Fig. 14, specific ssDNAs were first immobilized onto a magnetic microparticle surface. Consequently, sandwich assemblies were formed when target DNA hybridizes with both the magnetic particle probes and the bio-bar-coded AuNP probes. The magnetic separation of the sandwich complex followed by thermal dehybridization releases the free bar-code nucleotides, which was then subjected to analysis. This method has led to 500 zeptomolar sensitivity, which is comparable to many PCR-based approaches without the need for enzymatic amplification [92]. Additionally, multiplexed DNA detection is well suited with this system by using a mixture of different biobarcoded NP probes [93].

5. Detection of Microorganisms Using Nanoparticles

5.1. Fluorescence-Based Detection Using Nanoparticles

The efficient detection of pathogenic microorganisms is of great importance in food, medical, forensic, and environmental sciences [94]. AuNP-conjugated polymer systems were used to

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detect pathogens [95]. Three cationic AuNPs and one anionic PPE carrying carboxylate and oligo(ethylene glycol) arms were combined to generate non-covalent complexes. In the presence of bacteria, the initially quenched fluorescent polymers recover their fluorescence. The sensor array has been used to identify 12 microorganisms, which contain both Gram-positive (e.g. *A. azurea, B. subtilis*) and Gram-negative (e.g. *E. coli, P. putida*) species. As shown in Fig. 15, LDA discerns not only the species, but also the strains of the bacteria. The outstanding performance of this system is attributed to the exceptional quenching ability of AuNPs as well as the 'molecular wire' effect of PPE polymer [96].

The use of QDs as a fluorescence labeling system in microorganism detection has been successfully demonstrated [97]. Fluorescent CdSe NPs were conjugated with wheat germ agglutinin (WGA), which can respond to gram-positive bacteria [98]. In the presence of the bacteria, the QD-WGA conjugate can bind to sialic acid and N-acetylglucosaminyl residues on the bacterial cell walls. QDs can also be conjugated with antibodies to detect specific pathogenic microorganisms such as Escherichia coli, Salmonella typhimurium, Cryptosporidium parvum, Giardia lamblia, and oral bacteria [99,100,101,102]. QD-antibody systems have been shown to exhibit superior photostability and multiplexing capability, compared with traditional organic dyes. In addition, QDs conjugated with zinc-dipicolylamine (Zn-DPA) coordination complexes can selectively bind to a *Escherichia coli* mutant that lacks an O-antigen element, allowing optical detection in a living mouse leg infection model (Fig. 16) [103].

6. Conclusion and Future Prospects

NPs present a versatile synthetic scaffold for the creation of detection systems for analyzing chemical and biological targets. NPs provide a suitable platform for the incorporation of various receptors, allowing the binding of target analytes with appropriate affinity and selectivity. Moreover, the environment-sensitive optoelectronic properties of NPs can be harnessed to realize the transduction of the binding events. Thus, functionalized NPs can act as both molecular receptor and signal transducer, simplifying system design.

For many sensor applications NPs exhibit distinctive attributes that can increase the sensitivity and selectivity of assays relative to conventional diagnostic techniques. Advanced nanodiagnostic techniques have also opened a promising avenue to provide rapid, low-cost, easy and multiplexed identification of biomarkers (e.g. proteins and genes) in the clinic. However, to meet the demand of clinical diagnostics for the development of personalized medicine, continuous efforts for optimization of these parameters are necessary. In particular, efforts are required for the development of efficient sensors with the ability to detect analytes in complex biological fluids like blood, urine, serum etc. A crucial factor in designing highly efficient sensors is the modulation of nanoparticle surface functionality for selective capture of target analytes. For this purpose, nanoparticle surfaces have been engineered with suitable functionality to utilize the highly selective recognition events like formation of double-stranded DNA, antibody-antigen, and aptamer-analyte interactions. These systems are useful, but have limitations as regards sensing of disease states. This is mainly due to the need of a tremendous amount of pertinent recognition elements for the multianalyte detection. This issue is being addressed in two parallel fashions. In one case, miniaturization of the sensor system allows more specific binders to be used in a given device. The other possible direction is the use of a differential sensor array approach. As in this case selectivity is required rather than specificity, a limited number of individual sensors may screen unlimited number of different target analytes. To this end, although it is clear that the NPs provide a powerful and evolving toolkit for designing ultrasensitive detection methods, much work needs to be done for transition of these settings towards the real world applications.

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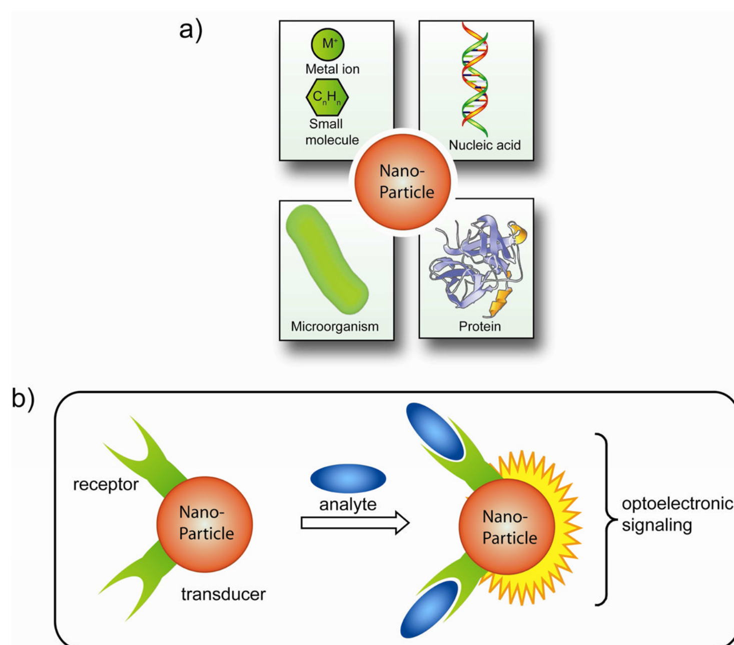

Fig. 1.
a) Examples of targets for nanoparticle based detection. b) Schematic depiction of a representative nanoparticle based detection system.

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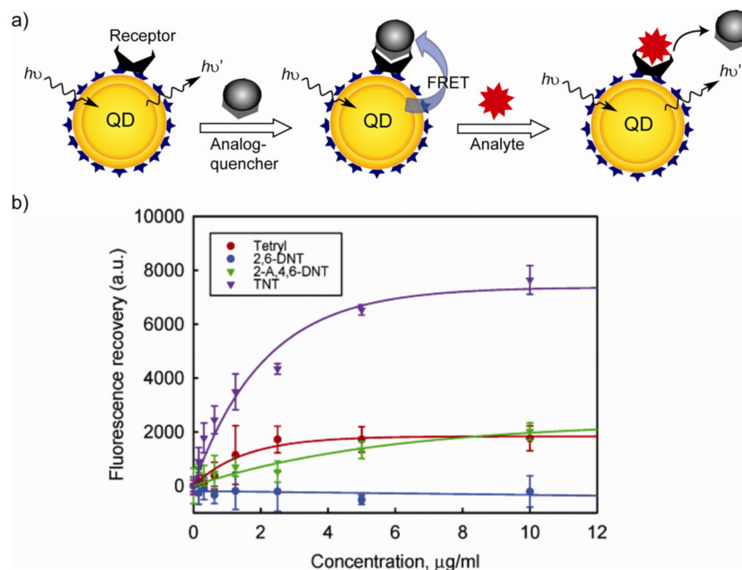

Fig. 2.

a) Schematic depictions of TNT sensor constructs. b) Specificity of the QD-based TNT sensor investigated in the presence of three TNT analogues (adapted with permission from reference [12]).

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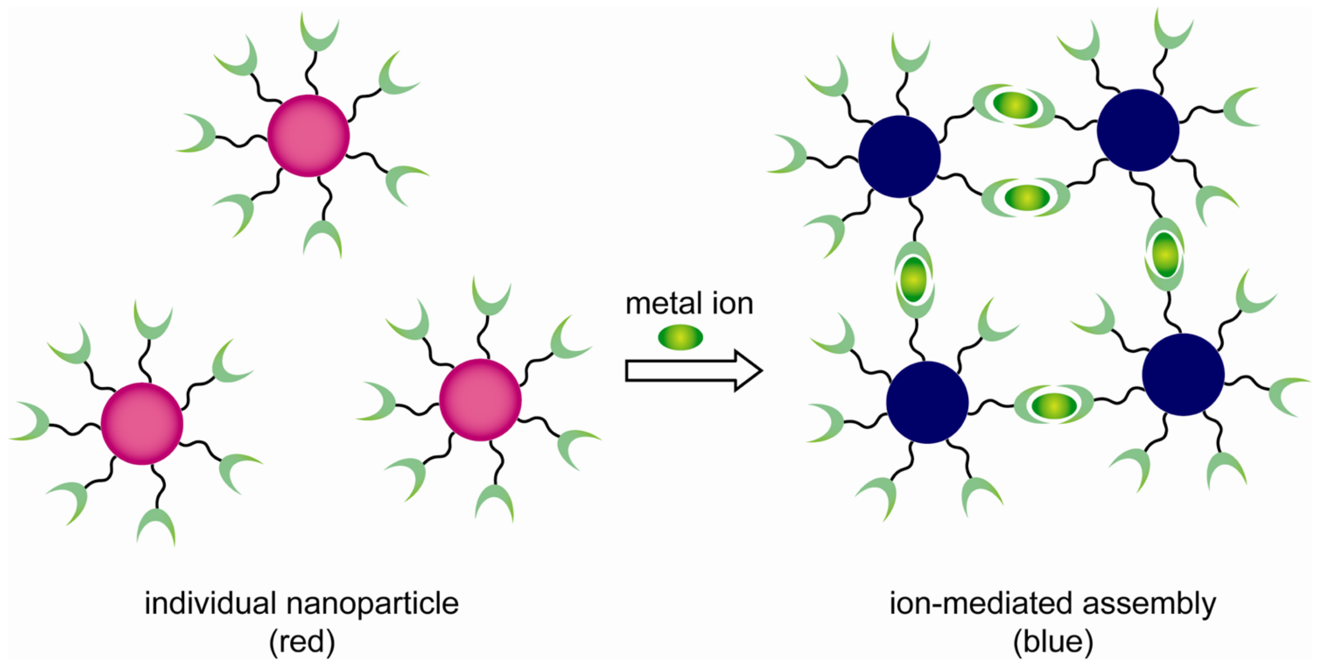

Fig. 3.
Schematic representation of metal ion-induced nanoparticle assembly.

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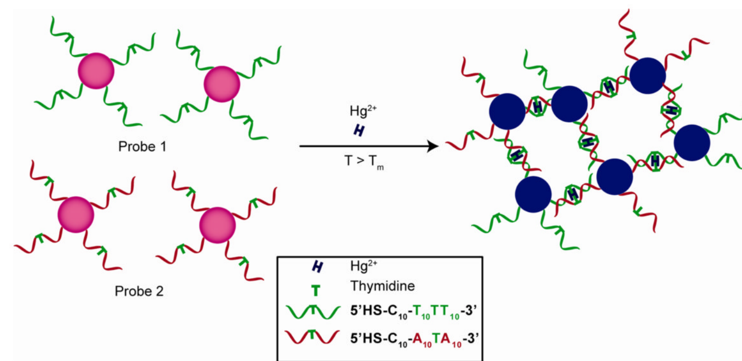

Fig. 4.
Hg^{2+} detection using DNA functionalized nanoparticle and relying on the thymidineHg^{2+}-thymidine coordination chemistry.

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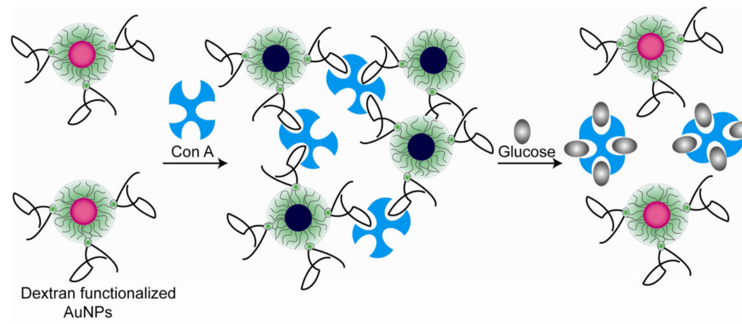

Fig. 5.
Glucose sensing using dextran functionalized nanoparticles.

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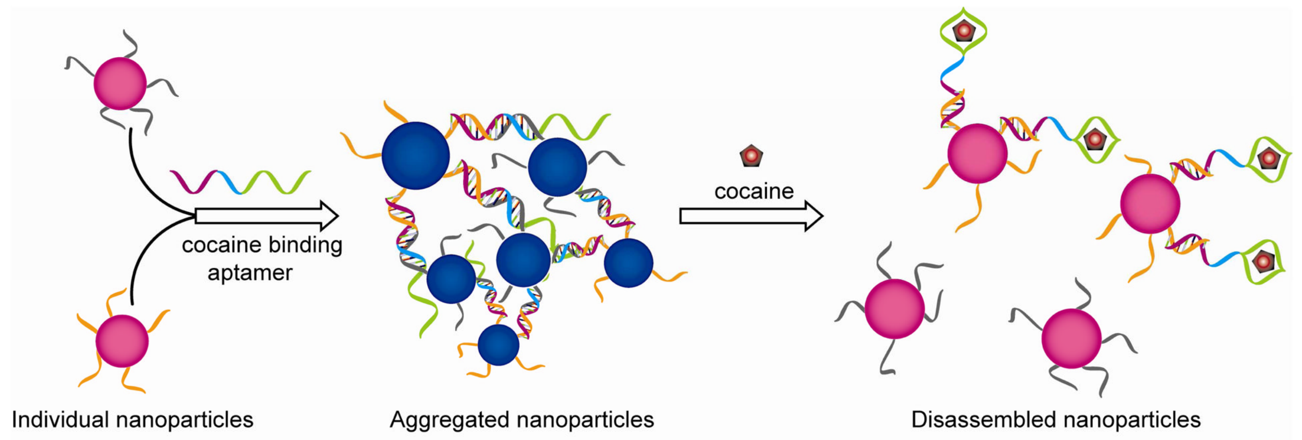

Fig. 6.
Aptamer mediated cocaine detection.

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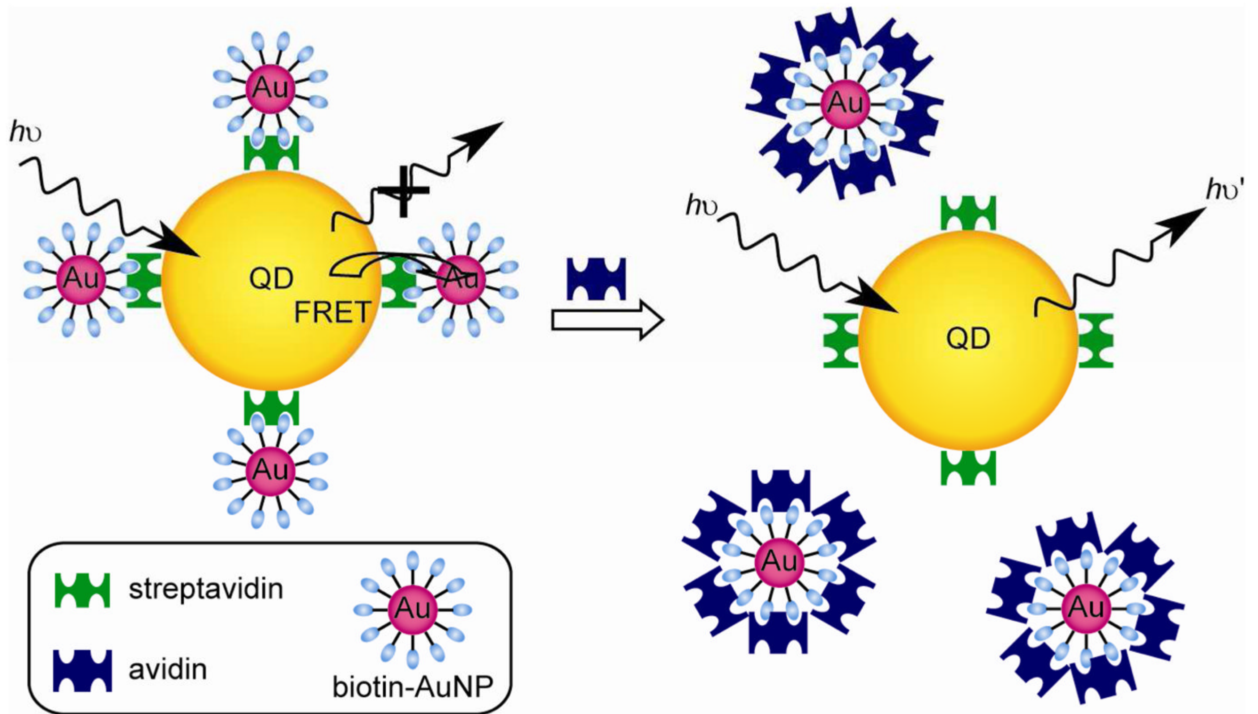

Fig. 7.
Assay for the detection of avidin by using QD-AuNP conjugate.

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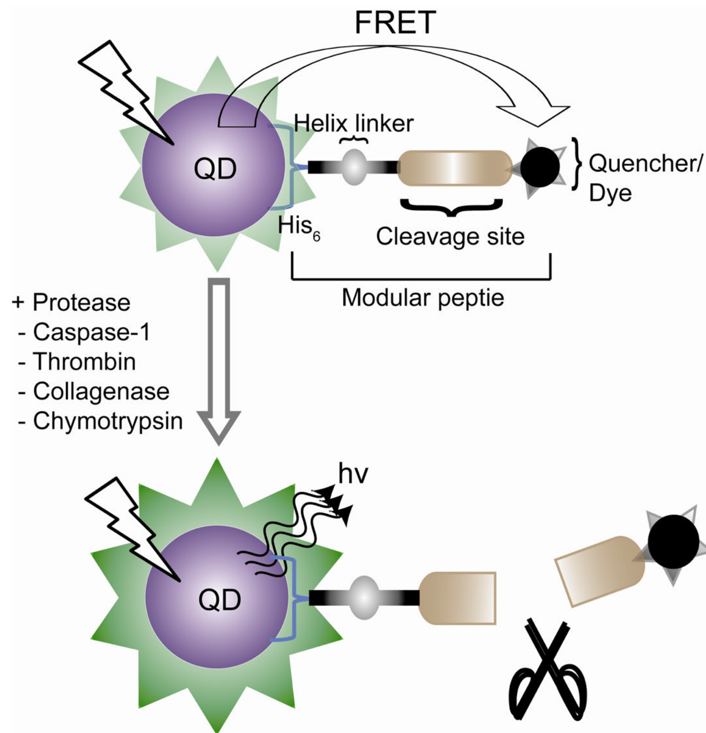

Fig. 8.
QD-Peptide sensor for proteases.

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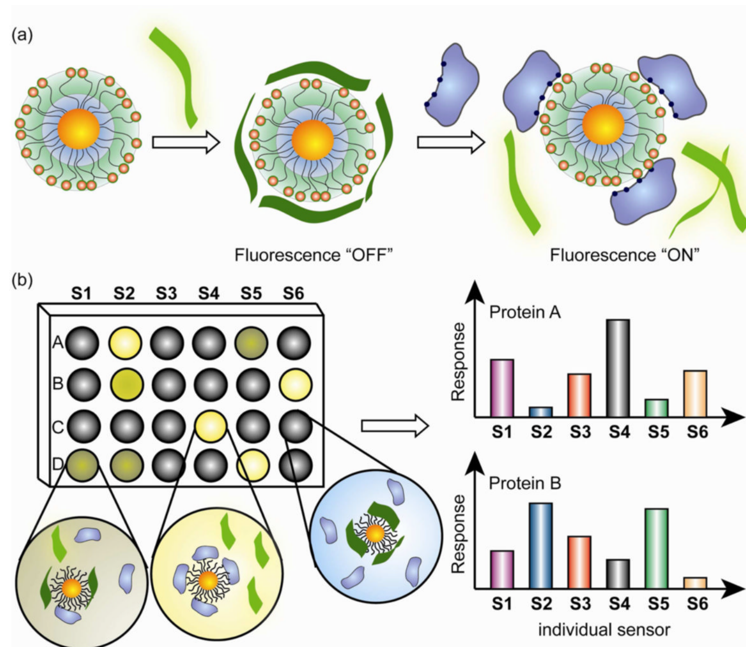

Fig. 9.
Illustration of 'chemical nose' sensor array. (a) The competitive binding between protein and polymer-NP complexes leads to the fluorescence recovery. (b) Fingerprint response patterns for individual proteins.

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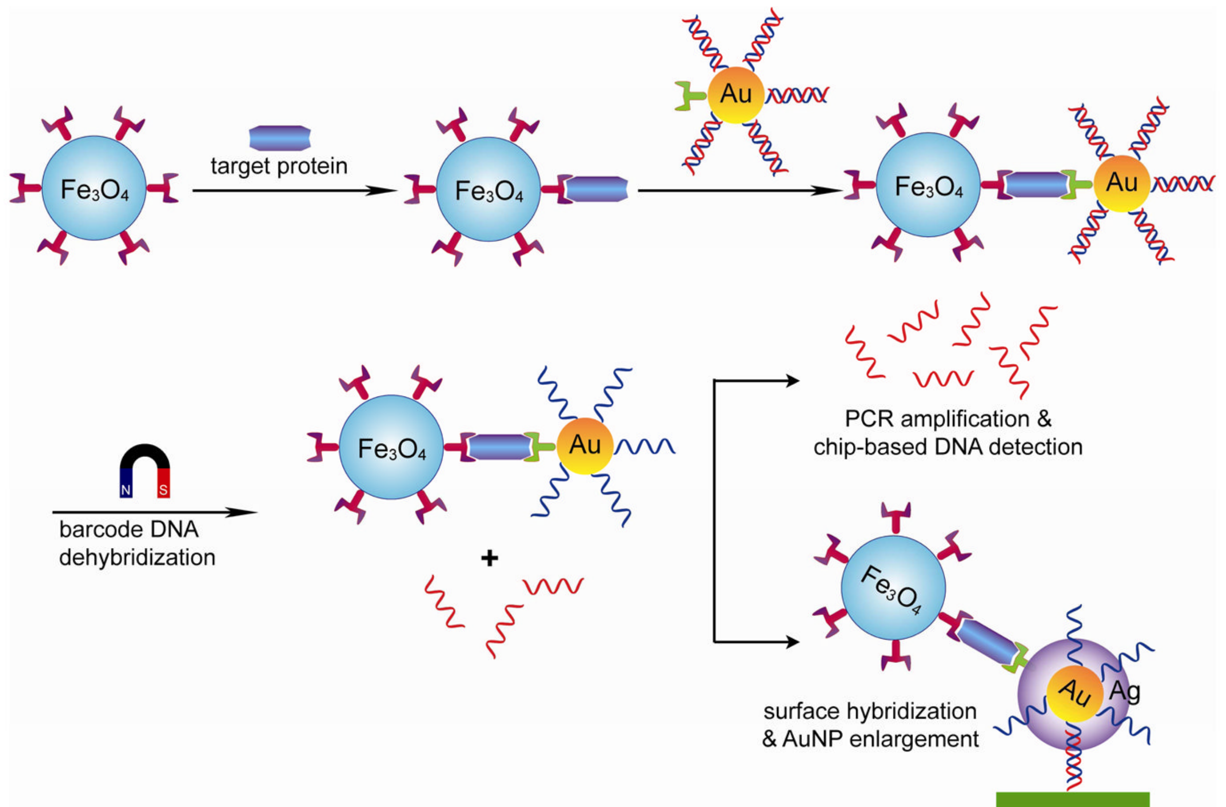

Fig. 10.
Nanoparticle based bio-bar-code assay for proteins.

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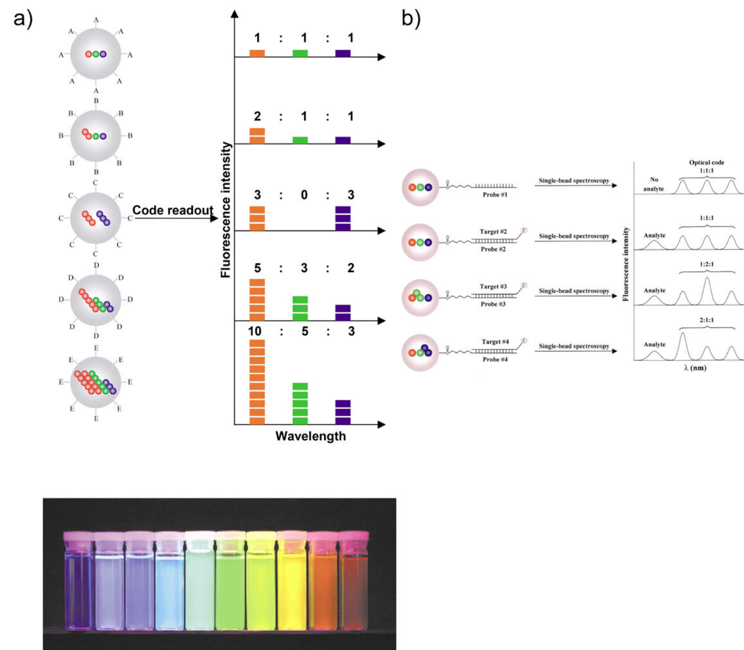

Fig. 11.
a) Fluorescence signature of microbeads with different ratios of QDs. b) DNA hybridization assay using microbeads. (adapted with permission from reference [60])

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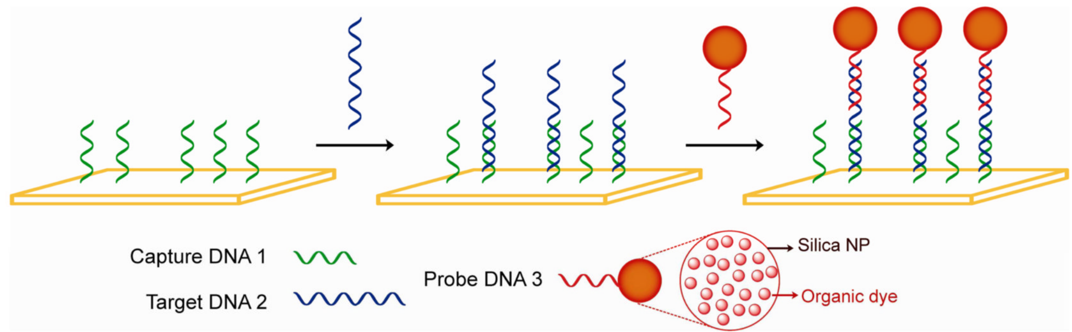

Fig. 12.
Bioconjugated silica NPs as labels for chip-based sandwich DNA assays.

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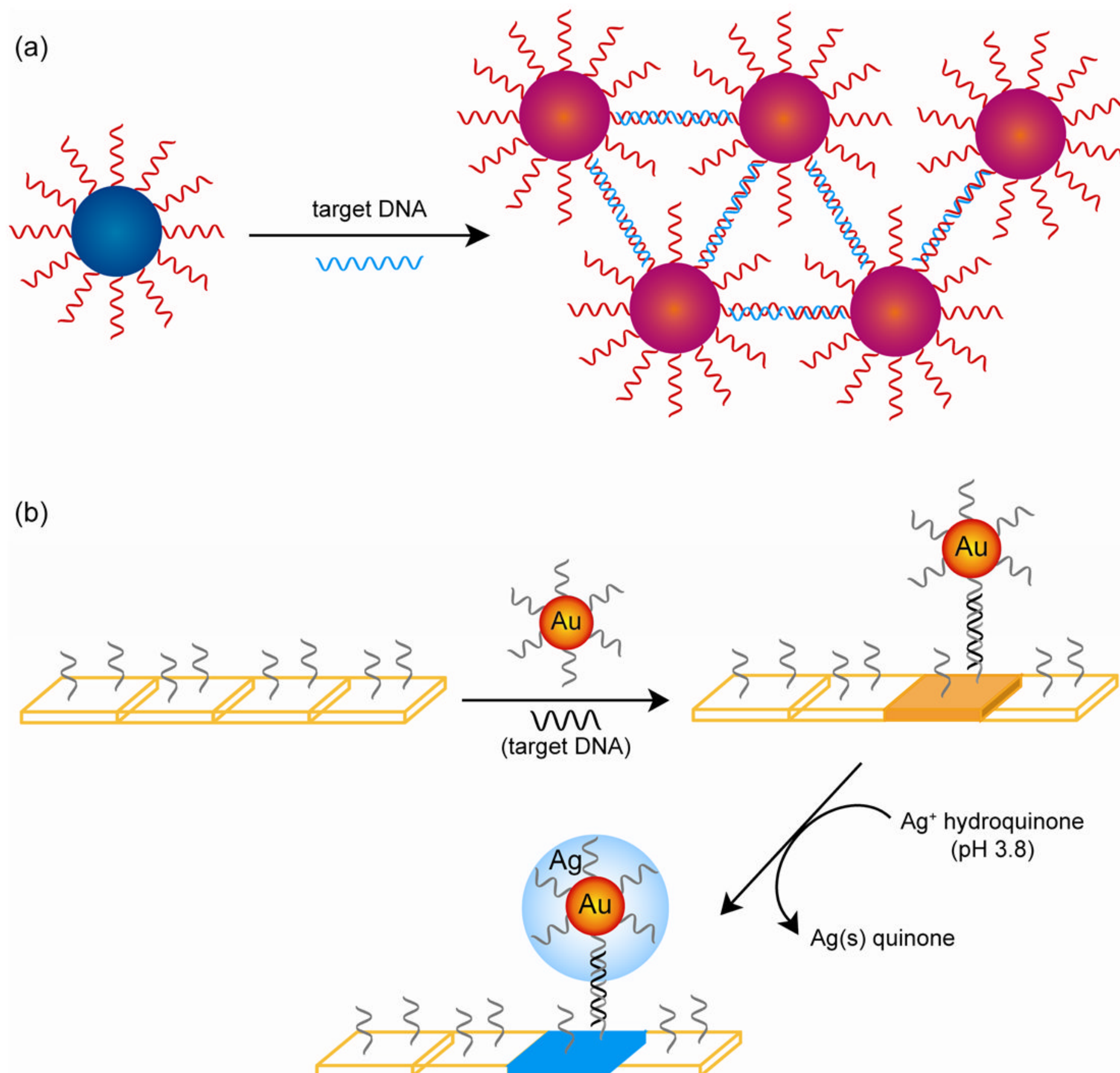

Fig. 13.
a) DNA mediated nanoparticle assembly. b) Chip-based system for DNA assay.

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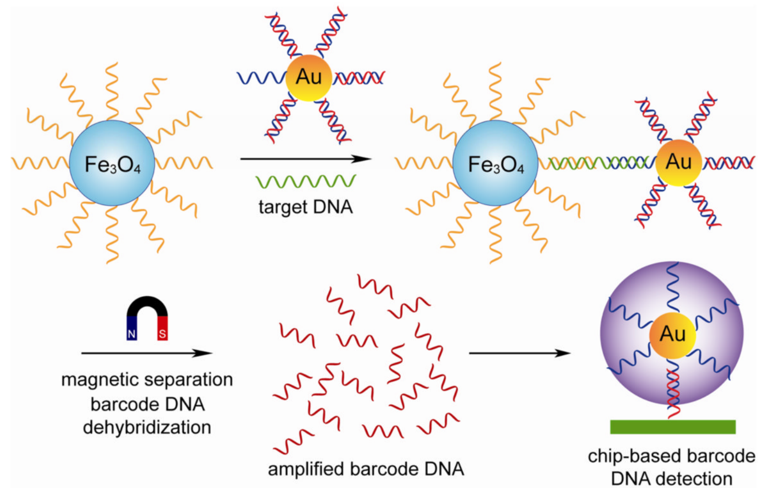

Fig. 14.
NP-based bio-bar-code assay of DNA

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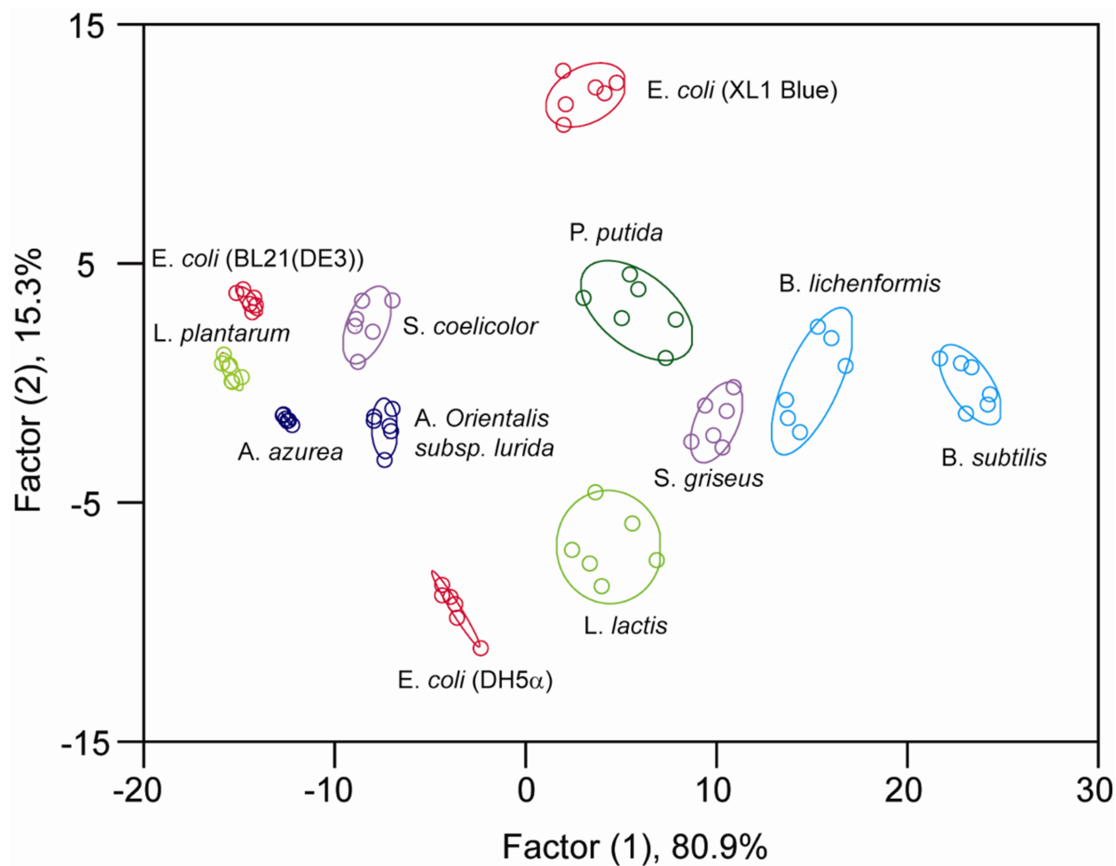

Fig. 15.

Canonical score plot for the fluorescence response patterns of three AuNP-conjugated polymer constructs in the presence of bacteria processed with LDA. The first two factors consist of 96.2% variance and the 95% confidence ellipse for the individual bacteria are depicted.

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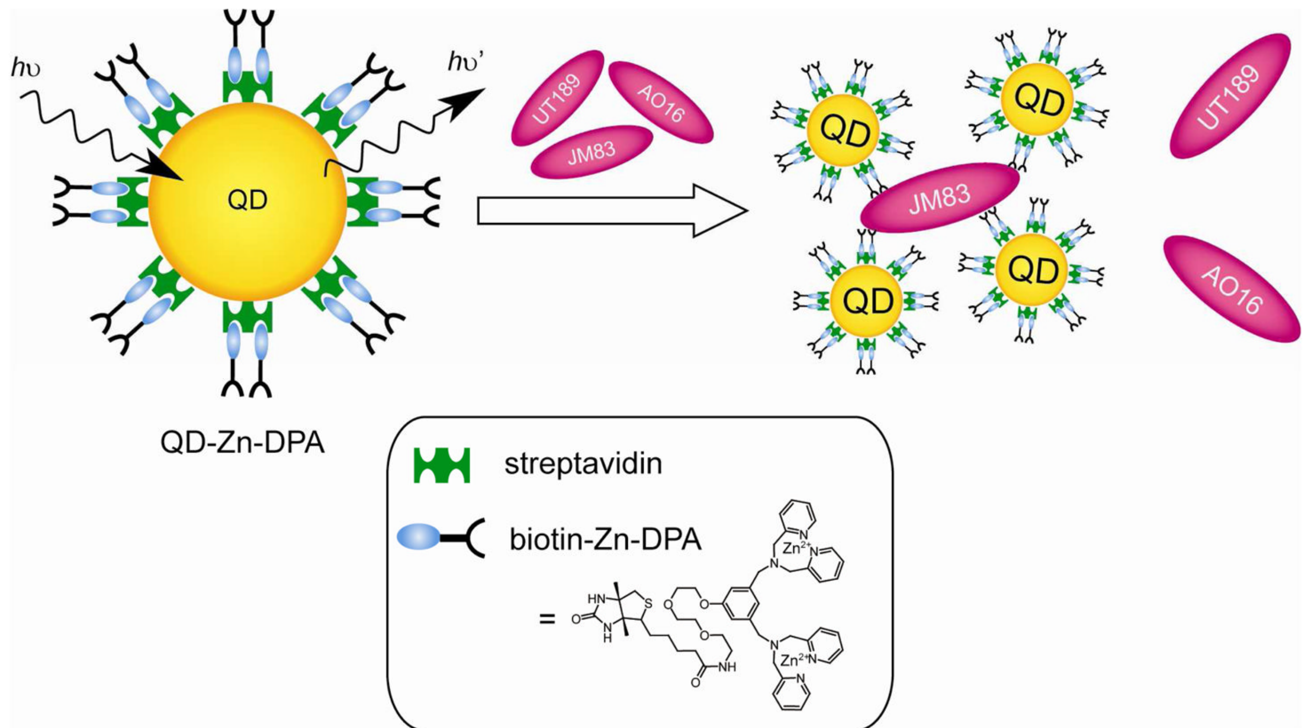

Fig. 16.
Schematic illustrations of QD-Zn-DPA and its selective detection to Gram-negative *E. coli* JM83.