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Gold Nanoparticles in Chemical and Biological Sensing

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1. Introduction

Detection of chemical and biological agents plays a fundamental role in biomedical, forensic and environmental sciences^{1–4} as well as in anti bioterrorism applications.^{5–7} The development of highly sensitive, cost effective, miniature sensors is therefore in high demand which requires advanced technology coupled with fundamental knowledge in chemistry, biology and material sciences.^{8–13}

In general, sensors feature two functional components: a recognition element to provide selective/specific binding with the target analytes and a transducer component for signaling the binding event. An efficient sensor relies heavily on these two essential components for the recognition process in terms of response time, signal to noise (S/N) ratio, selectivity and limits of detection (LOD).^{14,15} Therefore, designing sensors with higher efficacy depends on the development of novel materials to improve both the recognition and transduction processes. Nanomaterials feature unique physicochemical properties that can be of great utility in creating new recognition and transduction processes for chemical and biological sensors^{15–27} as well as improving the S/N ratio by miniaturization of the sensor elements.²⁸

Gold nanoparticles (AuNPs) possess distinct physical and chemical attributes that make them excellent scaffolds for the fabrication of novel chemical and biological sensors (Figure 1).^{29–36} First, AuNPs can be synthesized in a straightforward manner and can be made highly stable. Second, they possess unique optoelectronic properties. Third, they provide high surface-to-volume ratio with excellent biocompatibility using appropriate ligands.³⁰ Fourth, these properties of AuNPs can be readily tuned varying their size, shape and the surrounding chemical environment. For example, the binding event between recognition element and the analyte can alter physicochemical properties of transducer AuNPs, such as plasmon resonance absorption, conductivity, redox behavior, etc. that in turn can generate a detectable response signal. Finally, AuNPs offer a suitable platform for multi-functionalization with a wide range of organic or biological ligands for the selective binding and detection of small molecules and biological targets.^{30–32,36} Each of these attributes of AuNPs has allowed researchers to develop novel sensing strategies with improved sensitivity, stability and selectivity. In the last decade of research, the advent of AuNP as a sensory element provided us a broad spectrum of innovative approaches for the detection of

metal ions, small molecules, proteins, nucleic acids, malignant cells, etc. in a rapid and efficient manner.³⁷

In this current review, we have highlighted the several synthetic routes and properties of AuNPs that make them excellent probes for different sensing strategies. Furthermore, we will discuss various sensing strategies and major advances in the last two decades of research utilizing AuNPs in the detection of variety of target analytes including metal ions, organic molecules, proteins, nucleic acids, and microorganisms.

2. Synthesis and Surface Functionalization

Numerous preparative methods for gold nanoparticles have been reported, including both “top-down” (physical manipulation) and “bottom-up” (chemical transformation) approaches.³⁰ During the last two decades, considerable effort has been devoted to synthesis of AuNPs, focusing on control over their size, shape, solubility, stability and functionality. It is worth noting that the term colloid and cluster are frequently used interchangeably; the former generally refers to particles having diameter more than 10 nm, while the latter commonly refers to smaller particles.

2.1. Citrate and Related Particle Preparation Methods

The scientific synthesis of colloidal gold can be traced back to Michael Faraday’s work in 1857, in which the gold hydrosols were prepared by reduction of an aqueous solution of chloroaurate with phosphorus dissolved in carbon disulfide.³⁸ Later in 1951, Turkevich developed one of the most popular approaches for the synthesis of AuNPs, using citrate reduction of HAuCl_4 in water.³⁹ In this method, citric acid acts as both reducing and stabilizing agent and provides AuNPs in diameters of 20 nm. Further studies by Frens’ group enabled control of AuNPs size by varying the feed ratio of gold salt to sodium citrate.⁴⁰ The kinetics of the Turkevich process was provided by Chow and Zukoski.⁴¹ Detailed studies and evolution of the Turkevich reaction have been reported and employed in numerous applications.^{42–48}

2.2. The Brust-Schiffrin Method for Thiol-protected AuNPs

After Mulvaney’s initial attempt of stabilizing AuNPs with alkanethiols,⁴⁹ a significant breakthrough in the field of AuNPs synthesis was achieved by Brust and Schiffrin in 1994. They reported a two-phase synthetic strategy, (the Brust-Schiffrin method), utilizing strong thiol-gold interactions to protect AuNPs with thiol ligands (Figure 2). In this method, AuCl_4^- is transferred from aqueous phase to toluene using the surfactant tetraoctylammonium bromide (TOAB) and reduced by sodium borohydride (NaBH_4) with dodecanethiol.⁵⁰ On addition of NaBH_4 , a quick color change from orange to deep brown takes place in organic phase. The AuNPs are generated in toluene with controlled diameters in the range 1.5 to 5 nm. These thiol-protected AuNPs feature superior stability due to strong thiol-gold interaction and they can be easily handled, characterized and functionalized. The nanoparticles can be thoroughly dried and then redispersed in organic solvents without any aggregation or decomposition. Various reaction conditions, such as gold/thiol ratio, temperature, and reduction rate, can be used to tune the particle size.⁵¹ Immediate quenching

after reduction or use of sterically bulky ligands gives a higher portion of small core NPs (2 nm).^{52–56} With the translation of this synthesis into single-phase system,^{57–59} many modifications have been reported to obtain functional thiols-stabilized AuNPs. Isolable, water-soluble gold clusters protected by monolayers of tiopronin have been generated with an average core size of 1.8 nm.⁶⁰ Arenethiol ligands generate relatively larger and thermally less stable AuNPs than the alkanethiol protected clusters.⁵³ All-aromatic monolayer-protected clusters with potential value for enhanced rates of electron transfer can be synthesized by differential extraction of the poly-anionic products using benzenethiolates.⁶¹ Alkylthiosulfates (Bunte salts) can be used as ligand precursors to synthesize thiol-stabilized AuNPs⁶² and water soluble AuNPs at a larger size as well.^{63,64} AuNPs of mixed monolayer^{65,66} and single-component monolayer⁶⁷ of thymine moieties have been prepared for assembly studies via molecular recognition. A recent study on the identification and quantification of the precursor species in the Brust-Schiffrin method was also reported.⁶⁸ Superhydride⁶⁹, hexadecylaniline (inter alia)⁷⁰, organometallic reagents (2-propylmagnesium bromide)⁷¹, 9-borabicyclo[3.3.1]nonane (9-BBN)⁷² and glutathione⁷³ have been used as alternative reagents to NaBH₄ for the reduction of Au (III) in synthesis of thiol-protected AuNPs.

2.3. Place Exchange Method to form Mixed Monolayer AuNPs

Place exchange, i.e. substitution of thiol ligands by different thiols was reported by Murray *et al.*^{54,74,75} This versatile technique introduces chemical functionality onto AuNPs monolayer in a divergent fashion. In this method, the initially anchored thiol ligands are exchanged in by free thiol ligands (Figure 3, top). The reaction time and the feed ratio of the functional ligands control the loading efficiency onto AuNPs surface. Moreover, introducing two or more functional ligands during the place exchange reaction can provide mixed monolayer protected AuNPs for synergistic applications. The ligands on the AuNPs surface also interact with each other, leading to a rigid monolayer⁷⁶ and show a certain level of intra-monolayer mobility, providing optimization of the interaction with the analytes.⁷⁷ Under appropriate conditions, ligands can also slowly hop between NPs.⁷⁸ Place exchange is efficient for ultra-small 1.1 nm diameter phenylethanethiolate-stabilized AuNPs.^{79,80} Therefore, a range of functional groups can be employed in the synthesis of AuNPs by the use of functionalized thiols to place exchange with phosphine stabilized nanoparticles. (Figure 3, bottom).^{81,82}

2.4. Physical Methods for Particle Modification

Physical methods enable further manipulation of the structure and hence properties of AuNPs. Thermolysis,^{83,84} digestive ripening^{85,86} and conventional ripening^{87,88} have significantly reduced average particle size and polydispersity and triggered formation of superlattices in 2D and 3D. UV and laser irradiation are another parameter that can modify particle structure.^{89–94} Ultrasonic fields provide an approach to control the reduction rate of AuCl₄⁻ in aqueous solutions and therefore affect core sizes with the intensity of the ultrasound and the reactor position.^{95–100} Control of the particle size can also be provided by radiolysis.^{101–103} Once formed, size-exclusion chromatography can separate suspended AuNPs by shape and size.¹⁰⁴

2.5. Polymer Stabilized AuNPs

Polymer-stabilized AuNPs were first reported by Helcher in 1718, though of course the characterization was rather limited.¹⁰⁵ Polymers commonly used for stabilization include poly(*N*-vinylpyrrolidone) (PVP),^{106–108} poly(ethylene glycol) (PEG),^{109–112} poly(4-vinylpyridine),^{113–115} poly(vinyl alcohol) (PVA),¹¹⁶ poly(vinyl methyl ether) (PVME),¹¹⁷ chitosan,¹¹⁸ polyethyleneimine (PEI),¹¹⁹ poly(diallyl dimethylammonium chloride) (PDDA),¹²⁰ poly(methyl methacrylate) (PMMA),^{121,122} polystyrene-block polymers,^{123,124} poly(dG)-poly(dC),¹²⁵ and poly(*N*-isopropylacrylamide) (PNIPam).^{126,127}

There are four strategies widely used for creating polymer-functionalized nanoparticles. 1) The “grafting from” approach consists of polymer chain growth from small initiators attached to AuNPs.^{128–131} This technique generally provides a very dense polymer brush. Frequently used methods include living radical polymerization (LRP)¹²¹ and surface-initiated atom-transfer radical polymerization (SI-ATRP).^{113,132} 2) “Grafting to” enables one-pot synthesis of AuNPs stabilized by sulfur-containing polymers,^{133–139} and generally produces a sparser coverage.¹³⁴ 3) Physisorption using block copolymer micelles (nanoreactors), water-soluble polymers, or star block copolymers.^{140–146} 4) “Post-modification of pre-formed AuNPs”. In this method, AuNPs are generated in the first stage through conventional methods such as Brust-Schiffrin method, followed by the exchange or modification with polymers.^{147,148}

2.6. Other Capping Ligands

While most AuNP functionalization has been done using thiol/thiolated ligands, a variety of other ligands have been used to passivate and functionalize AuNPs. Other sulfur-containing ligands include disulfides,^{149–156} multivalent (and hence more stable) di-¹⁵⁷ and tri thiols,^{158,159} thioethers^{160,161} xanthates,¹⁶² and resorcinarene tetrathiols.¹⁶³ Iodine can be used to oxidize and decompose these thiol-stabilized AuNPs.¹⁶⁴ Amine-capped AuNPs were reported using primary amines.¹⁶⁵ Self-assembled gold(I) amine precursors including [AuCl(NH₂R)] (R=C₈H₁₇, C₁₂H₂₅ and C₁₆H₃₃) yield AuNPs upon decomposition through air exposure or in tetrahydrofuran (THF).^{166,167} Laurylamine (LAM) or octadecylamine (ODA) has been used to generate monodispersed particles.¹⁶⁸ Oleyl amine (OLA),¹⁶⁹ aromatic amines,¹⁷⁰ amino acids,^{171–175} diamines,¹⁷⁶ tetraoctylammonium¹⁷⁷, porphyrins¹⁷⁸ and hyperbranched polyethylenimine¹⁷⁹ have been used as reducing/capping agents in synthesis of AuNPs, while a direct one-pot synthesis of amine-stabilized AuNPs using 3-(trimethoxysilylpropyl)diethylenetriamine have been reported.¹⁸⁰ The controlled synthesis of AuNPs in quaternary ammonium ionic liquids by simple heating has been developed recently,¹⁸¹ and piperazine derivatives have been used as reducing/capping agents.¹⁸² Tri-*n*-octylphosphine oxide (TOPO), has been used in the presence of stabilizer octadecylamine.^{183,184} Studies using phosphine,^{185,186} carboxylate ligands,^{187–190} lactic acid,¹⁹¹ and hydroquinone¹⁹² as stabilizing ligands have also been documented.

3. Physical Properties

3.1. Size-dependent Electronic and Optoelectronic Properties

AuNPs possess quantum size effect that leads to discrete electron transition energy levels. For example, hexanethiol-functionalized AuNPs (Au_{147} , $d = 1.62$ nm) display 15 redox states at room temperature,¹⁹³ demonstrating that AuNPs can possess molecule-like redox properties.¹⁹⁴ Moreover, the quantized capacitance charging behavior of AuNPs can be tuned by external ligands, magnetic fields and electrolyte ions, leading to potential applications in electronic devices and electrochemical labels.^{195,196}

In addition to their redox activity, AuNPs feature a surface plasmon band (SPB).¹⁹⁷ The SPB is a result from the collective oscillation of the conduction electrons due to the resonant excitation by the incoming photons. This SPB is absent in both small AuNPs (< 2 nm diameter) and bulk gold. The nature of this surface plasmon resonance (SPR) was elucidated by Mie in 1908.¹⁹⁸ The SPR is influenced not only by size, but also by solvent, ligand, core charge, and temperature. Murray and co-workers has observed spectral shift induced by solvent refractive index changes that are consistent with Mie theory.¹⁹⁹ The refractive index dependence on solvent and ligand can alter the optical thickness, which can be used for detecting impurities due to different refractive indexes of gold oxide and gold chloride.²⁰⁰ The core charge, as mentioned above, is influential in determining SPB energy, causing shifts to higher energy with excess electronic charge and to lower one with electron deficiency.^{199,201–203} The mechanism of the dominant electronic dephasing was proposed to be that only electron-electron interactions were involved rather than electron-photon coupling.²⁰⁴ However, experimental data from femtosecond light scattering confirmed the occurrence of both processes in the individual AuNPs.²⁰⁵ Furthermore, the SPR frequency is sensitive to the proximity of other nanoparticles. Therefore, the aggregation of nanoparticles results in significant red-shifting (from ~ 520 nm to ~ 650 nm) and broadening in the SPB, changing the solution color from red to blue due to the interparticle plasmon coupling.^{206,207} This phenomenon has made AuNPs an attractive candidate for colorimetric sensors (*vide infra*).

A rough estimation of the nanoparticle concentration can be made based on the number of gold atoms and the molar extinction coefficient of colloidal gold ($\sim 4000 \text{ M}^{-1} \text{ cm}^{-1}/\text{gold atom}$).²⁰⁸ The extinction coefficients of AuNPs with different sizes and stabilizing ligands have been obtained experimentally.²⁰⁹ For example, AuNPs with 20 nm diameter have a molar extinction coefficient of $1 \times 10^9 \text{ M}^{-1} \text{ cm}^{-1}$, substantially higher than the organic dyes, indicating that AuNPs offer a superior light collecting efficiency.

3.2. Fluorescence Quenching

Early fluorescence studies on AuNPs focused on fluorescent ligands, such as pyrenyl,²¹⁰ polyoctylthiophenyl,²¹¹ fluorenyl,²¹² and other probes.^{213–216} Photoluminescence was reported later for water-soluble AuNPs.²¹⁷ AuNPs, however, also show enhancement in fluorescence at appropriate fluorophore-to-metal distances on solid substrates.²¹⁸ It is believed that this phenomenon is due to the reflected far-field radiation from the fluorophore back onto itself.

Fluorescence quenching is a commonly observed consequence when fluorophores are appended onto AuNPs. The resonant energy transfer has led to applications in biophotonics²¹⁹ and materials science.^{220–222} This quenching occurs when the emission spectrum overlaps with the gold surface plasmon band.^{223–225} Both radiative and non-radiative rates are particle dependent, with higher efficiencies of quenching occurring with small nanoparticles.^{226–229} A long-range molecular ruler, termed as nanosurface energy transfer (NSET), was demonstrated for breaking the “FRET barrier”.²³⁰ NSET is similar to FRET but is capable of measuring nearly 2-fold greater distances, making nanoparticles smaller than 2 nm of particular interest in bionanotechnology.^{231,232} Another process that quenches fluorophores is photoinduced electron transfer (PET) to nanoparticles that can be modulated by charging/discharging the gold core.^{233,234}

4. Colorimetric Sensing

The aggregation of AuNPs of appropriate sizes ($d > 3.5$ nm) induces interparticle surface plasmon coupling, resulting in a visible color change from red to blue at nanomolar concentrations.²⁰⁷ The color change during AuNP aggregation (or redispersion of an aggregate) provides a practical platform for absorption-based colorimetric sensing of any target analyte that directly or indirectly triggers the AuNP aggregation or redispersion.^{16,235,236}

4.1. Detection of Metal Ions

4.1.1. Alkali and Alkaline Earth Metal Ions—AuNP-based colorimetric sensing for metal ions generally requires the incorporation of chelating agents onto the nanoparticle surface. The presence of analyte ion induces the nanoparticle aggregation by forming multidentate interparticle complexes with the chelating ligand (Figure 4). For example, AuNPs carrying 15-crown-5 moieties have been fabricated for the colorimetric detection of potassium ions (K^+) via formation of a 2:1 sandwich complex between 15-crown-5 moiety and K^+ .²³⁷ Most attractively, this sensor system showed micromolar recognition and colorimetric response towards K^+ even in the presence of physiologically important cations, such as Li^+ , Cs^+ , NH_4^+ , Mg^{2+} , Ca^{2+} , and excess Na^+ . Later the performance of this sensor system was improved by bifunctionalizing the AuNPs with thioctic acid and crown thiols.²³⁸ The increased rate of K^+ recognition from this system has been attributed to a cooperative effect that allows crown moiety to be preorganized by the negatively charged carboxylate moiety of the thioctic acid for K^+ recognition. Utilizing this principle the analogous detection of Na^+ in urine has been achieved by incorporating 12-crown-4 onto the AuNP surface together with the thioctic acid.²³⁸ In a similar fashion Li^+ has been detected by utilizing phenanthroline-functionalized 4 nm AuNPs,²³⁹ and lactose-functionalized 16 nm AuNPs have been used to detect Ca^{2+} ²⁴⁰ through metal ion-mediated carbohydrate-carbohydrate interactions.

4.1.2. Heavy Metal Ions—Heavy metal ions such as Pb^{2+} , Cd^{2+} , and Hg^{2+} pose significant public health hazards. Hupp *et al.* have reported a simple colorimetric technique for the sensing of aqueous heavy metal ions utilizing 11-mercaptoundecanoic acid (MUA)-functionalized 13 nm AuNPs.²⁴¹ The color change (red to blue) is driven by heavy-metal ion

chelation process where the surface carboxylates act as metal ion receptors. Colorimetric response was observed from Pb^{2+} , Cd^{2+} , and Hg^{2+} (400 μM), whereas Zn^{2+} displays no response to this assay process. The ion driven aggregation process was also detected using the enhanced hyper-Rayleigh scattering (HRS) response from the nanoparticle aggregates, leading to a more sensitive (25 μM) detection of Pb^{2+} ion. Chang and coworkers have significantly improved the selectivity and sensitivity of this system by fine tuning of the buffer composition and monolayer structure,²⁴² achieving 100 nM sensitivity. A colorimetric sensor for Pb^{2+} was developed by Chen and coworkers that utilized mixed monolayer-protected AuNPs carrying both carboxylate and 15-crown-5 functionalities.²⁴³ In this system, initial aggregates of AuNPs were formed due to hydrogen bonding interactions between carboxylic acid residues in a methanol/water solvent system. Addition of Pb^{2+} disrupts 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. This system showed high sensitivity and selectivity over other metal ions including Cd^{2+} and Hg^{2+} . Colorimetric detection of Cu^{2+} and Hg^{2+} has been achieved using AuNPs decorated with cysteine and peptide functionality.^{244,245} Quaternary ammonium-functionalized AuNPs have been utilized by Liu *et al.* to devise a simple colorimetric sensor for Hg^{2+} at room temperature, with the abstraction of AuNP stabilizing thiols by Hg^{2+} inducing aggregation.²⁴⁶ Mirkin and coworkers have employed DNA-functionalized AuNPs for the selective and sensitive detection of Hg^{2+} .²⁴⁷ This thiolated-DNA based detection system relies on the thymidine- Hg^{2+} -thymidine coordination chemistry and the melting temperature (T_m) of the nanoparticle aggregates. For the assay, AuNPs were functionalized with two different thiolated-DNA sequences (designated as probe 1 and probe 2 in Figure 5). When mixed together, probe 1 and probe 2 form aggregates with lower T_m due to T-T mismatches in their base sequence. Presence of Hg^{2+} in the system raises the T_m of the AuNP aggregates through selectively coordinating with the T-T mismatches to form stable T- Hg^{2+} -T base pairs, providing detection down to 100 nM Hg^{2+} .²⁴⁷ However, this method requires an electronic heating element coupled with the sensor system for careful monitoring of T_m during the detection process. To avoid this need for heating during the read-out process Liu and coworkers have optimized the number of T units in the DNA strands so that the system operates at ambient temperature.²⁴⁸ Chang and coworkers have reported a visual Hg^{2+} sensing method based on Hg^{2+} -induced conformation change of a T-rich single-stranded DNA (ssDNA).²⁴⁹ Recently, simple thymine functionalized AuNPs have been employed for the colorimetric detection of Hg^{2+} ion.²⁵⁰ Specific interaction of Hg^{2+} with thymine residues from two AuNPs induces aggregation process and corresponding color change. Mirkin and coworkers have reported the discrimination of cysteine from other amino acids utilizing T- Hg^{2+} -T coordination chemistry and employing the DNA based probes.²⁵¹ AuNPs modified with 5,5'-dithiobis (2-nitrobenzoic acid) were also used for the detection of trace levels Cr^{3+} (99.6 ppb) in the presence of 15 other metal ions in aqueous solution.²⁵²

DNAzymes are DNA-based catalysts.^{253–258} Liu and Lu have fabricated highly selective lead biosensors using DNAzyme-directed assembly of AuNPs,^{259–262} allowing the tuning of sensitivity over several orders of magnitude. These DNAzymes were obtained through the combinatorial method systematic evolution of ligands by exponential enrichment (SELEX).

In their sensor design, a DNAzyme specific to the Pb^{2+} ion was chosen as the target recognition element and DNA-functionalized AuNPs were used as the signal transducer element. The Pb^{2+} -specific DNAzyme is comprised of an enzyme strand and a substrate strand. In the presence of Pb^{2+} ion, the enzyme strand carries out catalytic reactions involving hydrolytic cleavage of the substrate strand. When incubated with DNAzyme, the DNA-functionalized AuNPs form blue-colored assemblies through Watson-Crick base pairing as shown in Figure 6. The DNAzyme is activated in the presence of Pb^{2+} in the solution. Activated DNAzyme cleaves the substrate strand to dissemble the AuNPs, resulting in a blue-to-red color change. The sensor was capable of detecting Pb^{2+} concentration of 100 nM. More importantly, other divalent metal ions such as Ca^{2+} , Co^{2+} , Ni^{2+} , and Cd^{2+} did not induce any color change. Optimization to control the AuNP orientation in the assemblies allowed fast detection of Pb^{2+} (< 10 min) at ambient temperature.²⁶² Later, a highly selective and sensitive colorimetric sensor for uranyl (UO_2^{2+}) based on AuNP and UO_2^{2+} selective DNAzyme has been reported using both labeled and label-free methods.²⁶³

4.1.3. Other Metal Ions—Hutchison and coworkers have developed a sensitive and selective trivalent lanthanide (Ln^{3+}) ions sensor based upon tetramethylmalonamide (TMMA) functionalized AuNPs.²⁶⁴ The presence of Ln^{3+} ions in the AuNP solution initiates AuNP cross-linking and concomitant red to blue color change through the formation of 2:1 TMMA- Ln^{3+} chelating complex. An immediate colorimetric response to the Ln^{3+} ions was detected, with sensitivity down to ~50 nM for Eu^{3+} and Sm^{3+} . Recently, Wang and coworkers have devised a colorimetric method for detecting Al^{3+} based on pentapeptide (CALNN) functionalized AuNPs.²⁶⁵ The affinity of Al^{3+} towards the functional carboxylic group of the pentapeptide induces AuNP aggregation and color change. This assay was successfully applied for sensing of the Al^{3+} on living cellular surfaces under physiological conditions.

4.2. Detection of Anions

Numerous efforts have been devoted to the development of sensor system for anionic species.^{266–268} Designing recognition motifs for anions is challenging due to their lower charge to radius ratio, pH sensitivity, wide range of geometries, and solvent dependent binding affinity and selectivity.²⁶⁸ Kubo *et al.* have attached isothiuronium groups onto AuNP surface and demonstrated sensing of oxanions such as AcO^- , HPO_4^{2-} , and malonate in 10% (v/v) H_2O -MeOH solution.²⁶⁹ Colorimetric sensing of hydrophilic anions (e.g. dihydrogen phosphate) has been achieved in dichloromethane using AuNPs with phenyl urea anion binders.²⁷⁰ AuNPs coated with ethylene glycol-appended isothiuronium units were used to detect F^- in water using 3-nitrophenylboronic acid as a mediator at pH 5.5.²⁷¹ Ionic liquid functionalized AuNPs have been applied for anion sensing.^{272,273} For example, Itoh *et al.* have used ionic liquids based on the imidazolium cation for colorimetric sensing of I^- and PF_6^- .²⁷² AuNPs coated with thioglucose groups have been used by Watanabe *et al.* to sense fluoride anions over a relatively narrow concentration range (20 ~ 40 mM) in water,²⁷⁴ with high selectivity against other anions such as Cl^- , Br^- , I^- , AcO^- , and NO_3^- . Ahn *et al.* have reported selective sensing of trans-dicarboxylates such as fumarate (one of the key components generated in the Krebs cycle) over its cis-isomer, maleate utilizing

AuNPs functionalized with an anion-recognition motif.^{275,276} Utilizing this system, discrimination of benzene-1,4-dicarboxylate from its isomers benzene-1,2- and benzene-1,3-dicarboxylate in water was also possible.²⁷⁶

Fast and sensitive detection of CN^- is important for environmental monitoring and the evaluation of food safety.^{277,278} Han *et al.* reported a colorimetric detection method for cyanide anions in aqueous solution employing adenosine triphosphate-stabilized AuNPs and a Cu^{2+} -phenanthroline complex as the receptor unit.²⁷⁹ In their sensing ensemble, exposure of CN^- to Cu^{2+} -phenanthroline complex induced a decomplexation process to generate free phenanthroline, which subsequently caused the ATP-stabilized AuNPs to aggregate resulting in color change. Utilizing this system 10^{-5} M CN^- was detected in neutral aqueous solution. Han *et al.* have reported an AuNP-embedded plasticized poly(vinyl chloride) (PVC) membrane for sensing of iodide anions in the presence of F^- , Cl^- , Br^- , N_3^- , NO_2^- , NO_3^- and CH_3COO^- .²⁸⁰ Yuan *et al.* have employed AuNPs decorated with a zinc (II) dipicolylamine-phosphate binding group for the colorimetric detection of bis-phosphorylated peptides.²⁸¹ Li *et al.* have utilized a “click” reaction coupled with the AuNP probes for the visual detection of ascorbic acid.²⁸² Mirkin *et al.* have employed the Griess reaction (coupling of sulfanilamide and naphthylethylenediamine by nitrite) for the AuNP-based colorimetric detection of nitrite.²⁸³

4.3. Detection of Small Organic Molecules

Geddes *et al.* have demonstrated a competitive colorimetric glucose assay using assemblies of concanavalin A (Con A) and dextran-functionalized AuNPs.^{284,285} As shown in Figure 7, multivalent binding with Con A crosslinks dextran-coated nanoparticles. The presence of glucose in the system competitively binds Con A, releasing the dextran-coated AuNPs that can be readily monitored by either conventional UV/Vis spectrometry²⁸⁴ or wavelength-ratiometric resonance light scattering with a glucose dynamic sensing range of 1 – 40 mM.²⁸⁵ Due to the wide detection range, this system can potentially be useful to diagnose the blood glucose level in healthy people (3 – 8 mM) and in diabetics (2 – 40 mM). Molecularly imprinted polymers (MIP) with embedded AuNPs (Au-MIP) have been used by Sugimoto *et al.* as a colorimetric sensor for adrenaline.²⁸⁶ In the absence of adrenaline, the shrunken MIP gel provides close proximity of AuNPs. Adrenaline swells the MIP gel and causes a blue shift in the plasmon absorption band of the immobilized AuNPs, with a dynamic range from 5 μM to 2 mM. AuNPs surface functionalized with water-soluble copolymers [poly(N-n-isopropylacrylamide-co-acryloyldiethylethylenetriamine)] have been employed by Uehare *et al.* for the detection of glutathione.²⁸⁷ In their system, the AuNP aggregates form upon mixing the AuNP solution with the polymer. Addition of glutathione results in spontaneous disassembly of the aggregates with concomitant colorimetric response. AuNPs conjugated with thermoresponsive co-polymers have been utilized for the colorimetric sensing of thiol compounds.^{288,289} Recently, cysteamine-modified AuNPs have been employed for the colorimetric detection of melamine²⁹⁰ and 2,4,6-Trinitrotoluene (TNT)²⁹¹ in real world matrices.

Aptamers are single-stranded oligonucleic acid-based binding molecules that are generated by SELEX, an *in vitro* selection process.²⁹² These functional DNA or RNA structures can

bind a wide variety of targets with high affinity and specificity. Aptamer-based analytical methods have been used with the AuNP-based platform for colorimetric detection of small organic molecules.^{293–299} For example, an effective colorimetric adenosine sensor was designed by Lu and coworkers.²⁹³ As illustrated in Figure 8, the sensor is composed of nanoparticle aggregates containing three functional components: two kinds of ssDNA-modified AuNPs and a linker DNA molecule that carries adenosine aptamer. Initially, AuNPs and the linker DNA were suspended in solution to generate purple AuNPs. In the AuNP aggregation process, the linker DNA molecule pairs respectively with two ssDNA-functionalized AuNPs where a part of adenosine aptamer also takes part in the DNA hybridization process. When adenosine is present in the system, the aptamer changes its structure to bind with adenosine. This adenosine binding process results in the disassembly of the AuNP aggregates with a concomitant blue-to-red color change. Utilizing this system, adenosine was detected in concentrations from 0.3 to 2 mM. To demonstrate the generality of this system, Lu and coworkers have further constructed a colorimetric sensor for cocaine employing a cocaine aptamer.²⁹³ Interestingly, the use of a mixture of different aptamers provided smart materials with cooperative responses to adenosine and cocaine.²⁹⁴ The generality of the approach has been further demonstrated by introducing a third aptamer/nanoparticle component (responsive to potassium ions³⁰⁰) with this system. Lu and coworkers have also immobilized both adenosine and cocaine aptamer-linked nanoparticle aggregates onto a lateral flow device, resulting a more sensitive “dipstick” test which can be performed in complex sample matrices such as human blood serum.²⁹⁹ Stone *et al.* have reported an AuNP-based colorimetric detection system for theophylline using a theophylline recognizing aptamer.²⁹⁸ Recently, an aptamer-based colorimetric biosensor for Ochratoxin A (OTA) has been reported by Marty *et al.*²⁹⁶ Highly specific target recognition property of aptazymes has been utilized to devise colorimetric sensor for small organic molecules.³⁰¹ For example, Lu *et al.* have devised an adenosine biosensor based on the adenosine recognizing aptazyme-directed assembly of AuNPs.³⁰² RNA aptazyme-tethered AuNP was employed by Ogawa *et al.* for developing sensing system to visually detect ligands of a cleavase-like RNA aptazyme at room temperature.³⁰³ Gu *et al.* have employed a highly specific oxytetracycline binding ssDNA aptamer to discriminate oxytetracycline from other tetracyclines, such as doxycycline and tetracycline.³⁰⁴

4.4. Detection of Oligonucleotides

Detection of genetic mutations provides crucial target for diagnostics,^{305,306} while nucleic acid detection can be used to identify microbial pathogens. Fluorescent and radioactive detection readout methods (e.g. PCR, RT-PCR, northern blot, southern blot, and high density microarrays) are the conventional techniques for the detection of oligonucleotides.^{307–310} AuNP-based colorimetric assays have been demonstrated to be a highly competitive technology for oligonucleotide targets.^{311,312}

DNA-mediated AuNP assembly was demonstrated by Mirkin in 1996.³¹³ Fabrication of AuNPs functionalized with thiolated DNA strand allowed researchers to tailor the properties of the nanoparticle probes according to the assay method. This discovery has stimulated extensive use of oligonucleotide-directed AuNP aggregation for colorimetric detection of oligonucleotides^{311,314–321} and fabrication of structured assemblies.³²² In this approach, two

ssDNA-modified AuNP probes were used for colorimetric detection of target oligonucleotides. The base sequences in the AuNP probes are designed so they are complementary to both ends of the target oligonucleotides (Figure 9). AuNP aggregation with concomitant color change is triggered by the presence of target oligonucleotides as a result of hybridization of DNA strand. Highly specific base-pairing of DNA strands coupled with the intense absorptivity of AuNPs enables the sub-picomolar quantitative colorimetric detection of oligonucleotides.³¹⁷ Maeda *et al.* have shown that the aggregation of DNA-functionalized AuNPs can also be induced by hybridization of target DNA that does not cross-link the AuNPs,³²³ with an unusual sensitivity of this system towards single-base mismatches. Rothberg *et al.* have shown that citrate-stabilized AuNPs can discern ssDNA and double-stranded DNA (dsDNA) at the level of 100 fmol through simple electrostatic interactions.³²⁴ Mismatches even at the level of single base-pair have been easily detected through this way. A nearly “universal” sensing strategy employing an ssDNA probe, unmodified AuNPs, and a positively charged, water-soluble conjugated polyelectrolyte has been demonstrated by Xia *et al.* to detect a broad range of targets including DNA, proteins, small molecules, and inorganic ions.³²⁵

Another important application of oligonucleotide-directed AuNP assembly is for the colorimetric screening and triplex DNA binders.^{326,327} Screening of triplex DNA binders uses three components: two sets of AuNPs functionalized with non-complementary ssDNA strand and a free strand of ssDNA that can form triplex structure with the DNA (Figure 10).³²⁶ At room temperature, no aggregation of ssDNA functionalized AuNPs takes place due to the low stability of the triplex structure. However, the presence of appropriate triplex DNA binders (e.g. benzo[e]pyridoindole and coralyne (CORA)) stabilizes the triplex structure, inducing the AuNP aggregation and corresponding color change. The simplicity of this approach makes a convenient and high-throughput method for identifying triplex binders from large combinatorial libraries. Oligonucleotide-directed AuNP assembly has also been applied for determining the relative binding strengths of molecules to duplex DNA by colorimetric assay, providing a strategy for identifying DNA binding drugs.^{328,329}

4.5. Detection of Proteins

Many disease states (e.g. cancer) are often associated with the presence of certain biomarker proteins and/or irregular protein concentrations. AuNPs have been successfully applied for colorimetric detection of proteins. A diverse range of carbohydrate functionalized AuNPs have been prepared for the detection of carbohydrate binding proteins.^{330–340} For example, the aggregation of β -D-lactopyranoside (Lac)-functionalized AuNPs has been utilized by Kataoka *et al.* for the detection of *Recinus communis* agglutinin (RCA₁₂₀).³³⁸ The degree of colloidal aggregation was proportional to the protein concentration, thus allowing this method to be useful in quantitative detection of lectin. Significantly, a high sensitivity of lectin detection (lectin concentration of 1 ppm), has been achieved with this system.³³⁸ Later, the density of Lac moiety on the particle surface has been modulated for controlling the concentration range of lectin detection.³³⁹ The investigation showed that a critical Lac density (>20%) is required to trigger lectin-induced aggregation. The protein-directed assembly of gold glyconanoparticles has also been developed for facile and sensitive identification of protein-protein interactions. In an interesting study, binding partners of Con

A have been identified by utilizing the assemblies of Con A and mannose-modified AuNPs, since the protein-protein interactions disrupt the initial nanoparticle-protein assemblies.³⁴¹ Similarly, a series of gluco- and manno-oligosaccharide-functionalized AuNPs have been used to sense carbohydrate-protein using the lectin Con A.³⁴² Recently, a novel fluorescent based competition binding assay was also reported by Wang *et al.* to measure the binding affinity of glyconanoparticles (AuNPs conjugated with underivatized mono-, oligo-, and polysaccharides) with model protein (lectin Con A).³⁴³ Lactose-stabilized gold glyconanoparticles have been employed by Russell *et al.* to measure calcium ion-mediated carbohydrate-carbohydrate interactions.²⁴⁰ The controlled aggregation of lactose-stabilized ~16 nm AuNPs has been harnessed to obtain colorimetric detection of cholera toxin at nanomolar levels.³⁴⁴ AuNPs functionalized with a series of synthetic sugar probes have been utilized by Uzawa *et al.* for discriminating ricin toxin.³⁴⁵ By utilizing biotin-functionalized AuNPs deposited on glass substrates, label-free optical methods to study biomolecular interactions in real time has been developed by Chilkoti *et al.*^{346,347} Likewise, 15 nm sialic acid functionalized AuNPs have been employed to the optical detection of JC virus VLPs through sialic acid recognition.³⁴⁸

In an aptamer-based strategy, AuNP probes carrying platelet-derived growth factors (PDGFs)-specific aptamers have been employed by Chang *et al.* to detect PDGFs at nanomolar concentrations.³⁴⁹ Additionally, by conducting a competitive binding assay, this aptamer-AuNP-PDGF assembly has been used to detect PDGF receptors.³⁴⁹ Dong *et al.* have reported an even simpler aptamer-based colorimetric protein sensing method using unmodified AuNP probes.³⁵⁰ In their sensor design, unmodified AuNPs were initially stabilized with thrombin-binding aptamers. In the presence of thrombin, the aptamers fold into a G-quadruplex/duplex structure due to the aptamer-protein recognition. As the aptamers fold, their relatively rigid structure induces AuNP aggregation with a detection limit of 0.83 nM. Likewise, glass surfaces have been modified with thrombin-specific aptamer to achieve thrombin sensing.³⁵¹ Since thrombin includes two binding sites for the aptamer, this process leads to a “sandwich” complex. Later, this method was extended by further enlargement of the immobilized AuNPs in a growth solution containing HAuCl₄, CTAB, and NADH.³⁵² This process initiates the SPR coupling interactions between the adjacent AuNPs, and provided sensitivity limit of 2 nM for thrombin. A general antigen-antibody interaction has also been applied for the AuNP aggregation-based immunoassay for proteins.³⁵³ Utilizing this method, Rosenzweig *et al.* have demonstrated a detection limit of 2 µg/mL of anti-protein in serum samples.³⁵⁴

Dithiols cross-link AuNPs,³⁵⁵ with dithiol-functionalized peptides affording a useful platform for colorimetric detection of proteases.³⁵⁶ Scrimin *et al.* have designed two C- and N-terminal cysteinyl derivatives of peptide substrates specific to thrombin and lethal factor.³⁵⁷ For their assay, the peptides were first treated with the analytes. Subsequently, the solution was incubated with citrate-stabilized 12 nm AuNPs. Nanoparticle aggregation was induced by the intact peptides in the absence of target proteases, whereas the protease-cleaved peptides do not bridge the AuNPs. Later, Stevens *et al.* further simplified this two-stage approach by employing AuNPs decorated with Fmoc-protected peptides that bear a cysteine anchor.³⁵⁸ Presence of thermolysin in the system cleaved the peptide ligands,

leading to AuNPs dispersion in the solution along with a blue-to-red color change (Figure 11). An impressive sensitivity of 90 zg mL^{-1} (less than 380 molecules) has been reported from this system. Based on the enzymatic cleavage of DNA molecules, Mirkin *et al.* have developed a real-time colorimetric screening method for endonuclease activity by using DNA-mediated AuNP assemblies.³⁵⁹ Simultaneous determination of the efficiencies of endonuclease inhibitors (e.g. molecules with DNA-binding ability) has been achieved utilizing the colorimetric endonuclease-inhibition assay. Similarly, detection of kinase,³⁶⁰ phosphatases,^{361,362} β -lactamase,³⁶³ and aminopeptidase³⁶⁴ along with the screening of their activity have been achieved utilizing the enzyme-triggered AuNP assembly/disassembly approach. Zare *et al.* have demonstrated a colorimetric sensor for protein conformational changes by utilizing AuNP probes.³⁶⁵

5. Fluorescence-based Sensing

5.1. FRET-based Detection of Metal Ions and Small Molecules

AuNPs can serve as excellent fluorescence quenchers for FRET-based assays²²³ due to their extraordinary high molar extinction coefficients and broad energy bandwidth.³⁶⁶ Murray and coworkers have reported a FRET based assay for the detection of various metal ions.³⁶⁷ Electrostatic complexation of anionic tiopronin-coated AuNPs and $[\text{Ru}(\text{bpy})_3]^{3+}$, a well-known cationic fluorophore, results in fluorescence quenching of $[\text{Ru}(\text{bpy})_3]^{3+}$. The complexes then can be dissociated by addition of electrolytes and the fluorescence of $[\text{Ru}(\text{bpy})_3]^{3+}$ restored. AuNP FRET quenching has been utilized in Hg^{2+} sensing.³⁶⁸ Chang *et al.* reported that selectivity of the optimized Rhodamine B-absorbed AuNPs system for Hg^{2+} is 50 times higher than that of other metal ions (e.g. Pb^{2+} , Cd^{2+} , Co^{2+}) with a detection limit of 2.0 ppb. A FRET based Cu^{2+} ion sensor has been developed using bispyridyl perylene bridged AuNPs by Zhu and collaborators.³⁶⁹ In the absence of the Cu^{2+} ion, the fluorescence of the bispyridyl perylene on AuNPs is quenched. The Cu^{2+} ions then replace the bispyridyl perylene from the AuNPs, restoring fluorescence. Thomas *et al.* have used lanthanide complexes of bipyridine-functionalized AuNPs as phosphorescent sensors for alkaline earth metal ions and transition metal ions.³⁷⁰

Besides detecting metal ions, FRET based AuNP assays have been utilized for sensing small organic molecules. Chang *et al.* have used AuNPs in which Nile red non-covalently attached to AuNPs for sensing thiols at submicromolar levels.³⁷¹ As another example, Tang *et al.* have designed a FRET based cholesterol sensor by using β -cyclodextrin (β -CD) functionalized AuNPs.³⁷² Inclusion of fluorescein (FL) into cavity of CD on AuNPs causes complexation of AuNP-CD-FL construct, resulting in fluorescence quenching of FL through FRET. In the presence of cholesterol, FL inside CD is replaced by the cholesterol due to their higher binding affinity to CD, restoring FL fluorescence for detection of cholesterol at nanomolar concentrations. FRET based AuNP assays have also been reported for detecting homocysteine.^{373,374} Due to strong fluorescent properties of AuNP smaller than 1.2 nm, AuNPs have been used to detect metal ions and proteins, using aggregation induced quenching or enhanced fluorescence of AuNPs.^{375–378}

5.2. AuNP-based Molecular Beacons

Hairpin FRET-based systems for sensing DNA have been created by labeling molecular beacons with AuNPs.²¹² As shown in Figure 12, the nucleic acid probe conjugated with the organic dye is self-complementary, forming the hairpin structure on AuNP with effective FRET fluorescence quenching. The hairpin structure changes to rodlike through complementary hybridization with the target DNA, resulting in an increase in fluorescence of the dye. By employing similar principle, Nie *et al.* have shown that single stranded oligonucleotide-functionalized AuNPs with fluorophore-termini can assemble into a constrained arch like conformation.³⁷⁹ In this conformation, the fluorophore is efficiently quenched by AuNP due to close donor and acceptor distance. Upon binding with the target DNA, the constrained conformation opens and the fluorophore is separated from the AuNP, affording fluorescence turn-on. AuNPs based FRET assay have also been used to monitor the cleavage of DNA by nucleases.²³¹

Mirkin *et al.* have developed AuNP probes, (nano-flares) that are designed to detect and quantify intracellular analytes e.g. mRNA in cells.^{380–382} Hybridization of dye-terminated DNA reporter sequences with oligonucleotide-functionalized AuNPs quenches fluorescence of the reporter. The presence of a target then displaces and releases the reporter from AuNPs by constructing more stable duplex between the target and the oligonucleotide on AuNPs. Bai *et al.* have fabricated a FRET based AuNP assay to identify organic molecules that stabilize G-quadruplexes.³⁸³ Initially, AuNPs carrying fluorescein-tagged probe DNA quench the fluorescence of the probe. Upon specific binding of a target organic molecule, intramolecular folding of the linear probe DNA into G-quadruplexes formation increases the distance between the AuNP and the probe DNA with concomitant enhancement of fluorescence. Fan *et al.* have reported multicolor fluorescent AuNP-based molecular beacons to detect target molecular analytes.³⁸⁴ In their system, the multicolor dye-labeled aptamers are duplexed with DNA probes on AuNPs through complementary hybridization, resulting in fluorescence quenching of the dyes. In the presence of target molecules, the dye-labeled aptamer-target molecule binding separates the duplex, leading to fluorescence recovery of the dyes. FRET based AuNP assay labeled with fluorescence probes has also been reported to detect Hg²⁺.³⁸⁵

5.3. Sensors based on FRET between QDs and AuNPs

Semiconductor quantum dots (QDs) have been utilized for FRET-based AuNPs assays for detection of proteins, utilizing the high efficiency and stability of these fluorophores.³⁸⁶ Malvin *et al.* have reported a fluorescent competitive assay for DNA identification using QDs and AuNPs, where AuNPs were assembled with CdSe QDs through short complementary DNA strands, causing fluorescence quenching of the CdSe QDs.³⁸⁷ Addition of complementary oligonucleotides then displaces the AuNP-DNA from the QD-DNA, resulting in QD fluorescence restoration. Similarly, Kim *et al.* have fabricated an enzyme inhibition assay using biotinylated AuNPs and streptavidin-coated QDs as a FRET donor-acceptor couple (Figure 13).³⁸⁸ The biotinylated AuNPs specifically bind with the streptavidin-functionalized QDs forming quenched assemblies. The presence of avidin then releases the biotinylated AuNPs from QDs through a competitive binding with the biotinylated AuNPs. The authors have also demonstrated an approach for the rapid and

simple detection of protein glycosylation by using dextran-functionalized QDs and Con A-coated AuNPs.³⁸⁹

Yu *et al.* have used assembly of Con A conjugated QDs and β -CD-modified AuNPs for determination of glucose in serum.³⁹⁰ In practice, β -CD-modified AuNP is displaced by glucose due to its higher binding affinity to β -CD than Con A, resulting in release of Con A-conjugated QDs and recovery of QD fluorescence. Guo *et al.* have designed an inhibition assay for identification of Pb^{2+} based on the modulation in FRET efficiency between QDs and AuNPs.³⁹¹ Initially, the positively charged QDs form FRET donor-acceptor assemblies with negatively charged AuNPs by electrostatic interaction. The presence of Pb^{2+} aggregates AuNPs via an ion-templated chelation, inhibiting the FRET process, with a detection limit of 30 ppb of Pb^{2+} . Lu *et al.* have reported that simultaneous colorimetric and fluorescent detection of adenosine and cocaine in a single solution with QD-encoded aptamer sensors.³⁹²

5.4. “Chemical Nose” Approach for the Detection of Proteins, Pathogens and Mammalian Cells

The above FRET based assays employ specific interactions. Array-based sensing, i.e. “chemical nose/tongue” strategies provides a useful alternative that uses differential selective interactions to generate patterns that can be used to identify analytes or changes in complex mixtures.⁸ Recently, Rotello *et al.* have developed a protein sensor using chemical nose technology.³⁹³ The prototype sensor array was generated using six cationic AuNPs of differing structures and an anionic poly (*p*-phenyleneethynylene) (PPE) polymer. As illustrated in Figure 14a, electrostatic complexation of AuNPs and polymer results in fluorescence quenching of the polymer (fluorescence “OFF”) through energy transfer. Addition of protein analytes then disrupts the quenched polymer-AuNPs complexes via competitive binding, causing fluorescence recovery of the polymer (fluorescence “ON”). The protein-nanoparticle interactions are differential,^{394,395} leading to a fingerprint fluorescence response pattern for individual proteins (Figure 14b) that was characterized using linear discriminate analysis (LDA). By employing the same principle, an AuNP-green fluorescent protein construct was used to detect and identify proteins at 500 nM in undiluted human serum (~1 mM overall protein concentration)(Figure 14c).³⁹⁶

Analogous AuNP-conjugated polymer systems have been used to detect and identify bacteria.³⁹⁷ Three cationic AuNPs and one anionic PPE polymer were used to generate the sensor. Presence of bacteria disrupts the initially quenched assemblies leading to fluorescence restoration of PPE. From the distinct fluorescence response patterns, the sensor array was capable of identifying 12 bacteria including both Gram-positive (e.g. *A. azurea*, *B. subtilis*) and Gram-negative (e.g. *E. coli*, *P. putida*) species, as well as three different strains of *E. coli* (Figure 15).

The AuNP-conjugated polymer systems have been used for rapid and effective differentiation between normal, cancerous, and metastatic cells.^{398–400} The fluorescence responses analyzed by LDA were capable of distinguishing (i) different cell types; (ii) normal, cancerous and metastatic human breast cells; and (iii) isogenic normal, cancerous and metastatic murine epithelial cell lines (Figure 16).

Rotello *et al.* have also reported an enzyme-AuNP sensor array for detecting proteins in which the sensitivity is amplified via enzymatic activity.⁴⁰¹ In this system, cationic AuNPs are combined with β -galactosidase (β -Gal) through electrostatic interaction, inhibiting the β -Gal enzymatic activity. Addition of analyte proteins releases the β -Gal from AuNPs and restores the β -Gal activity, providing an amplified readout of the binding event (Figure 17).

6. Electrical and Electrochemical Sensing

AuNPs feature excellent conductivity, high surface area and catalytic properties⁴⁰² making them excellent materials for electrochemical^{15,403–418} In this section, we will summarize the use of AuNPs for electrocatalytic and electrochemical sensing.

6.1. Vapor Sensing

The electronic properties of self-assembled films of monolayer-protected AuNPs can be varied by tuning the particle size, interparticle separation, surface functionality, and chemical environments.⁴¹⁹ Chemiresistors are solid-state devices that rely on this sensitivity through changes in electrical resistance upon interaction with a chemical species. Over the past decade, there have been a number of chemiresistor vapor sensors based on thiol functionalized AuNPs.^{420–426} For example, Wohltjen and Snow have fabricated a chemiresistor by deposition of a thin film of octanethiol-coated AuNPs ($d \sim 2$ nm) onto an interdigitated microelectrode.⁴²⁷ A rapid decrease in the conductance due to film swelling was observed in presence of toluene and tetrachloroethylene, with a detection limit of ca. 1 ppm. Later, Shen and coworkers have shown that aromatic-functionalized AuNPs exhibited different sensory responses depending on the nature of the terminal functionality (OH, CH₃, NH₂, COOH) of aromatic thiols.^{428,429}

Vossmeier *et al.* have systematically investigated the sensing of toluene and tetrachloroethylene using films consisting of dodecylamine-stabilized AuNPs and α, ω -dithiols with different chain lengths (C₆, C₉, C₁₂, C₁₆).⁴³⁰ At a given concentration of toluene, it was observed that the resistance responses increase exponentially with increase of $-\text{CH}_2$ units. This effect was attributed to the augmentation of sorption sites with increasing ligand length. Zhong and coworkers have proved the correlation between the vapor-response sensitivity and the interparticle spacing properties.^{146,431} Recently, Wieczorek and coworkers successfully detected dissolved organic analytes using a thin film of hexanethiol protected AuNPs inkjet-printed onto microelectrodes.⁴³² On exposure to toluene, dichloromethane, and ethanol dissolved in 1 M KCl solution, an increase in impedance at 1 Hz was observed with detection limits of 0.1, 10, and 3000 ppm, respectively. Further studies by this group revealed that morphology, ionic strength and hydrophobic-hydrophilic character of nanoparticle film play an essential role in sensing.^{433,434}

Mixed monolayer surfaces of AuNPs have been used to develop ‘electronic-tongue’ type sensor arrays by varying the ratios of the different ligands on the nanoparticle surface.^{435,436} For example, AuNPs of two different thiol ligands have been fabricated by Kim *et al.*⁴³⁶ that showed different chemical selectivities and produced rapid and reversible responses towards the vapors of 1-propanol, acetone and cyclohexane. AuNP-dendrimer composites have also been explored in vapor sensing.^{437–441} In these layer-by-layer (LBL)

self-assemblies, the AuNPs provide the conductive film material while the dendrimers serve to cross-link the nanoparticles and to provide sites for the selective sorption of analyte molecules. An interesting bioconjugate material has been synthesized by simple reaction of the spider silk with aqueous chloroauric acid.⁴⁴² The environment-dependent expansion/contraction phenomenon of spider-silk modulates electron transport between nanoparticles, differentiating the polarity of alcohol vapors (from methanol to butanol) by distinct conductivity changes.

6.2. Electronic AuNP Sensors Employing Macrocyclic Complexation

The synergistic combination of electroactive AuNPs and macrocyclic compounds provides useful sensor systems.^{443–446} Willner and coworkers have constructed nanostructured assemblies via electrostatic cross-linking of citrate-stabilized AuNPs (12 ± 1 nm) and oligocationic cyclophanes (molecular squares). The assembly process was repeated in a stepwise manner to attain LBL assembly of anionic AuNPs and oligocationic cyclophanes (Figure 18). For sensing, the bipyridinium cyclophanes serve as π -acceptors⁴⁴⁷ for the association of π -donor substrates such as hydroquinone in their cavities, generating an electrochemical response.⁴⁴⁸ The sensitivity of the resulting sensor can be tuned via the number of assembled layers on the conductive surface.⁴⁴³ The binding affinity between the macrocycles and the analytes determines the selectivity of the electrodes, with cyclobis(paraquat-*p*-phenylene) cyclophane responding to hydroquinone, while the enlarged cyclophane cyclobis(paraquat-*p*-biphenylene) responds only to dihydroxymethyl ferrocene.⁴⁴⁶ Sensing studies with anionic π -donor analytes such as 3,4-dihydroxyphenylacetic acid and an acyclic crosslinker *N,N'*-diaminoethyl-4,4'-bipyridinium were also performed.⁴⁴⁵ Willner and coworkers have also developed a sensing interface by assembling a film consisting of polyethyleneimine, AuNPs and cyclobis(paraquat-*p*-phenylene) on the Al_2O_3 insulating layer of an ion-sensitive field-effect transistors.^{449,450} This device is able to sense charged analytes that are attached to the cyclophane, regardless of their redox activity. Detection of adrenaline was accomplished by measuring either the source-drain current or the gate-source voltage, with a detection limit of 1×10^{-6} M.⁴⁵⁰

6.3. AuNPs as Platforms for Electrocatalytic and Electrochemical Sensors

AuNPs feature catalytic activity that results from their large surface area-to-volume ratio and their interface-dominated properties.^{451–454} AuNPs can decrease the overpotentials of many electroanalytical reactions and maintain the reversibility of redox reactions.⁴⁵⁵ Numerous approaches such as electrostatic interaction,^{443–446} electrochemical deposition,^{456–460} and mixing with components in a composite electrode matrix,⁴⁶¹ have been applied to deposit AuNPs on electrode surfaces. For example, AuNPs have been used as electrochemical enhancers for electrogenerated chemiluminescence (ECL) sensors.^{462–464}

6.3.1. Detection of Small Molecules—AuNPs has been used for enhanced electrochemical detection of numerous small molecules^{465–477} including glucose,^{478–487} dopamine,^{488–493} uric acid,^{494–500} ascorbic acid,^{496–498,501–504} epinephrine,^{500,505–508} bisphenol A,⁵⁰⁹ nitrite,^{510–513} etc. Identification of several phenolic compounds;⁵¹⁴ e.g. catechol,⁵¹⁵ and aliphatic dicarboxylic acids; oxalic, succinic, malic, and tartaric⁵¹⁶ were also reported. For example, Wang and coworkers have electrocatalytically detected

epinephrine using a self-assembled dithiothreitol(DTT)-dodecanethiol(DDT)-Au colloid modified gold electrode. The electrode reaction of epinephrine is significantly improved at the nano-Au electrode, providing a detection limit of 60 nM.⁵⁰⁶ Recently, Luczak reported a voltammetric sensor for detection of norepinephrine using AuNPs, cystamine (CA) and 3, 3'-dithiodipropionic acid (DTDPA) modified gold electrodes. Moreover, the system is able to detect norepinephrine in presence of interferents ascorbic and uric acids.⁵¹⁷ Further, Zhang *et al.* have reported the superior electrocatalytic activity of positively charged AuNPs over negatively charged AuNPs using 4-dimethylaminopyridine (DMAP) coated AuNPs/L-cysteine film on gold electrode. Compared with electrodes modified by negatively charged AuNPs/L-cysteine, or L-cysteine alone, the electrode modified by the positively charged AuNPs/L-cysteine exhibited enhanced electrochemical behavior toward the oxidation of biomolecules such as ascorbic acid, dopamine and hydrogen peroxide.⁵¹⁸

6.3.2. Detection of Toxic Chemicals and Drugs—AuNP-based electrodes have been used to detect toxic ions such as arsenic,^{519–524} mercury,^{519,525–528} antimony,⁵²⁹ and chromium^{530,531}. Several groups also reported high catalytic activity of AuNP-modified electrodes for electrocatalytic oxidation and detection of carbon monoxide,^{532,533} nitric oxide,^{534–539} and hydrazine.^{540–544} Hydrogen peroxide (H₂O₂) was detected using AuNP decorated electrodes through enzymatic,^{545–555} non-enzymatic,^{556–560} and microfluidic electrochemical⁵⁶¹ approaches. Various pesticides, e.g. atrazine,⁵⁶² methyl parathion,^{563,564} paraoxon ethyl,⁵⁶⁵ carbofuran,⁵⁶⁴ phoxim,⁵⁶⁴ and different drugs such as paracetamol,^{504,566} atenolol,⁵⁶⁷ prednisolone,⁵⁶⁸ ethamsylate,⁵⁶⁹ were also detected using AuNP-modified electrodes. Recently, Raj has detected isoniazid, a popular anti-tuberculosis drug, by chemisorbing 70–100 nm AuNPs on a sol-gel-derived 3D silicate network with a detection sensitivity of 0.1 nM.⁵⁷⁰

6.3.3. Detection of Mammalian Cells using AuNP-modified Electrodes—AuNPs/chitosan nanocomposite gels were used for electrochemical monitoring of adhesion, proliferation, and apoptosis of cells on electrodes. Living cells immobilized on glassy carbon electrode (GCE) demonstrated an irreversible voltammetric response and enhanced the electron-transfer resistance with a limit of detection of 8.71×10^2 cells/mL.⁵⁷¹ Later, K562 leukemia cells were immobilized onto a microporous cellulose membrane modified with AuNPs and the effectiveness of anti-tumor drug methotrexate effect was monitored through the electrochemical response from cells.⁵⁷² Similarly, living pancreatic adenocarcinoma cells were immobilized on a composite electrode using AuNPs and carbon paste and used to determine the cytotoxic effect of antitumor drug adriamycin.⁵⁷³ Recently, de la Escosura-Muiz *et al.* have developed an electrocatalytic platform/sensor for the specific identification of tumor cells. In their system, molecules on cell surfaces are recognized by antibodies conjugated with AuNPs (Figure 19) with catalytic hydrogen reduction used to provide cell detection.⁵⁷⁴

6.4. AuNP-based Electrochemical Enzymatic Biosensors

6.4.1. AuNPs act as “Electron Wires” facilitating Direct Electron Transfer—The direct electrical communication of redox enzymes with electrodes is a useful strategy for biochemical sensing.⁵⁷⁵ However, the redox center of most oxidoreductases is electrically

insulated by the protein. AuNP-based electrodes acting as “electron wires” can facilitate direct electron transfer between redox proteins and bulk electrode materials, thus allowing electrochemical sensing without redox mediators,^{576–585} exploiting the physical properties of AuNPs.^{586–589} One practical method to develop AuNP-based enzyme electrodes uses immobilization of the enzyme on AuNPs deposited directly on the surface of the bulk electrode.⁵⁹⁰ Different strategies have been applied to immobilize enzymes onto AuNPs, such as direct attachment by the use of cysteine,⁵⁹¹ via thiol linkers,⁵⁹² and through covalent bonds.⁵⁹³ The co-deposition of redox enzymes and AuNPs on the electrode surfaces reduces the insulating effect of protein shell providing an excellent biosensor platform^{594,595} to detect various biomolecules.^{596–602} Moreover, adsorption of biomolecules onto AuNPs surface can preserve their bioactivity using biocompatible AuNPs.^{603,604} Again, the immobilization of enzymes onto AuNPs can increase their turnover rates,^{605–607} enhancing sensitivity. Willner and coworkers have constructed a gold nanoparticle based bioelectrocatalytic system with highly efficient electrical contact of glucose oxidase (GOx) with the electrode support. In their system, electron transfer between the enzyme active sites and the electrode support was facilitated through the reconstitution of apo-glucose oxidase (apo-GOx) on a 1.4 nm AuNP-functionalized with the cofactor flavin adenine dinucleotide (FAD) (Figure 20).⁶⁰⁸ The resulting AuNP-reconstituted enzyme electrodes featured high electron-transfer turnover rate of $\sim 5000 \text{ s}^{-1}$ (seven-fold higher than that of native GOx). This approach was further explored to pyrroloquinoline quinone (PQQ)-dependent enzymes by the reconstitution of apo-glucose dehydrogenase (GDH) on a PQQ-functionalized AuNP-modified gold electrode.⁶⁰⁹ Kerman *et al.* have demonstrated a streptavidin-coated AuNP-based sensing strategy to monitor protein phosphorylation.⁶¹⁰

Hemoglobin (Hb) has been extensively studied as a redox protein for direct electron transfer to AuNP-modified electrodes. Hb has very slow electron transfer rate to bulk electrodes, however, AuNPs can greatly enhance the electron transfer between Hb and electrodes with⁶¹¹ or without redox mediator.^{612–622} Yuan has used this system for amperometric sensing of H_2O_2 using Hb immobilized on multiwall carbon nanotubes (MWCNT)/AuNPs⁶²³ and onto AuNPs/MWCNT/chitosan composite matrices⁶²⁴ on GCE surface. Amperometric nitrite sensors have used Hb immobilized on AuNP-modified screen printed electrode⁶²⁵ and onto one-dimensional AuNP assemblies.⁶²⁶ Similarly, direct electrochemistry of myoglobin (Mb), an oxygen transporter in muscle tissues, was used to detect H_2O_2 using a variety of AuNP-modified electrodes.^{627–631} Also, an electrochemical H_2O_2 biosensor was created by immobilizing Mb and colloidal AuNPs onto Nafion-modified GCE. The immobilized Mb exhibited excellent electrocatalytic response to the reduction of H_2O_2 with a detection limit of $0.5 \mu\text{M}$.⁶³²

Direct electron transfer to electrodes of P450 enzymes, CYP2B6⁶³³ and CYP11A1⁶³⁴ were applied to detect drugs and cholesterol respectively. Similarly, the electrocatalytic activity of cytochrome c immobilized on AuNP-modified electrodes^{635,636,637} was used to sense H_2O_2 . LBL assembly methods based on electrostatic interaction have been employed to interface redox proteins by facilitating direct electron transfer.^{638,639} For example, multilayer films of GOx/AuNPs on gold electrodes using cysteamine as a covalent cross-linker were prepared by LBL technique. The bioelectrocatalytic response was directly correlated to the number of

deposited bilayers.⁶⁴⁰ Chen *et al.* have reported a H₂O₂ biosensor following the similar approach based on HRP immobilization on an LBL assembly of films of AuNPs and toluidine blue that responded rapidly to H₂O₂ with a detection limit of 70 nM.⁶⁴¹ Zhu and coworkers have fabricated the composite C@SiO₂ with AuNPs (AuNPs-C@SiO₂) by LBL assembly technique to sense H₂O₂.⁶⁴² Cobalt hexacyanoferrate-modified AuNPs were alternated with poly(vinylsulfonic acid) layers on indium tin oxide (ITO) electrodes and used as a platform for immobilization of GOx in the presence of bovine serum albumin (BSA) using glutaraldehyde as a cross-linker. This hybrid electrode successfully measured amperometric response of glucose at 0.0 V vs saturated calomel electrode (SCE).⁶⁴³

6.4.2. Enzyme Biosensors using AuNPs Composite Electrode Matrices—The incorporation of nanomaterials into composite electrode matrices presents another approach to enzyme biosensors, providing low background currents, straightforward surface generation, and the ability to incorporate of different substances into the bulk electrode matrix. AuNP-based composite electrode matrices have been used to detect phenol,⁴⁶¹ hypoxanthine,⁶⁴⁴ H₂O₂,^{645,646} atenolol,⁶⁴⁷ glucose,⁶⁴⁸ etc. Similarly, tyrosinase biosensors consisting of composite graphite-Teflon electrodes modified with AuNPs have been developed by Pingarrón *et al.* to detect different alkyl- and chlorophenols. The presence of AuNPs in the composite matrix increased the kinetics of the enzyme reaction and the electrochemical reduction of *o*-quinones at the electrodes, thus allowing nanomolar detection of phenolic compounds.⁶⁴⁹

AuNPs are often conjugated to other nanomaterials to improve their binding efficiency on electrode matrices.^{650–653} Electrodes featuring AuNPs conjugated with carbon nanotubes (CNT) provide excellent electrocatalytic ability⁶⁵⁴ enabling electrochemical biosensors for detection of glucose,^{655–659} cytochrome c,⁶⁶⁰ tryptophan,⁶⁶¹ hydroxylamine,⁶⁶² bisphenol A,⁶⁶³ etc. For example, an electrochemical sensor platform was constructed by covalent integration of AuNPs and CNTs onto a poly(thionine) modified GCE. Using HRP, the synergistic effect of the combined matrix in the presence of redox polymer mediator provided faster electron transfer and higher enzyme immobilization efficiency for detection of H₂O₂.⁶⁶⁴

6.4.3. AuNP/Polymer Matrices for Novel Electrochemical Biosensors—

Electropolymerization provides a strategy for biomolecule immobilization on the electrode surfaces in the presence of AuNPs. For example, Au-polypyrrole,⁶⁶⁵ Au-polyaniline,⁶⁶⁶ and AuNP-(3-mercaptopropyl)-trimethoxysilane (MPS) nanocomposite⁶⁶⁷ bioelectrodes have been fabricated to detect glucose as an analyte. AuNPs were assembled onto an AgCl@polyaniline nanocomposite-modified GCE, providing an amperometric glucose biosensor based on GOx. The hybrid electrode system showed superior electrocatalytic activity and reproducibility, detecting glucose at 4 pM.⁶⁶⁸ Similarly, an AuNP/polyaniline/AgCl/gelatin matrix has been successfully used for glucose biosensing.⁶⁶⁹ A H₂O₂ biosensor has been created by electropolymerization of *p*-aminobenzene sulfonic acid using cyclic voltammetry. In this approach, AuNPs were assembled in an interface containing amine groups of thionine followed by HRP adsorption and the resulting biosensor responded to H₂O₂ with a detection limit 0.64 μM.⁶⁷⁰ Zhu *et al.* have reported the use of an AuNP/

nafion/polythionine/gelatin matrix on Pt disk electrodes to immobilize HRP for H₂O₂ sensing.⁶⁷¹ Recently, a surface molecular self-assembly strategy for molecular imprinting in electropolymerized polyaminothiophenol (PATP) membranes at the surface of AuNPs modified GCE was reported for the electrochemical detection of the pesticide chlorpyrifos (CPF).⁶⁷²

Several groups have used the biopolymer chitosan to immobilize enzymes due to its biocompatibility and high mechanical strength. Using this approach, amperometric biosensors have been fabricated including GOx^{673–678} to detect glucose, HRP^{598,679–685} to detect H₂O₂, tyrosinase⁶⁸⁶ to detect phenolic compounds, acetylcholinesterase (AChE) to measure drug sensitivity⁶⁸⁷ or malathion activity⁶⁸⁸ were developed. A novel *in situ* interfacing of AuNPs with a chitosan hydrogel was achieved by one-step electrochemical deposition of tetrachloroauric (III) acid and chitosan on gold electrodes (Figure 21).⁶⁸⁹ The deposited interface showed excellent biocompatibility and stability. With AChE as a model enzyme, rapid amperometric sensing of the pesticides malathion and monocrotophos was achieved with a detection limit of 1 ng/mL.

6.5. AuNP-based Electrochemical Detection of Oligonucleotides

The unique electronic/electrochemical properties of AuNPs provide an alternative platform to optical sensing of oligonucleotides,^{690–698} providing an efficient tool for immobilizing DNA on electrodes⁶⁹⁹ as well as a label to signal the hybridization event.^{700–702} For example, an oligonucleotide with a mercaptohexyl group at the 5'-phosphate end was attached onto an AuNP-modified gold electrode, increasing nucleic acid loading efficiency to 1×10^{14} molecules/cm², ~10 times higher than a bare gold electrode.⁷⁰³ A variety of AuNP-based DNA sensing strategies (Figure 22) have been developed, including AuNP dissolution by acid,^{704–708} direct detection of AuNP/DNA conjugates anchored onto sensor surfaces,^{709–711} and AuNPs as carriers for other electroactive labels.^{712–717} Sensing enhancement by precipitation of silver^{718–726} and gold⁷²⁷ onto AuNPs labels have been used to achieve amplified signals. Recently, Bonanni *et al.* have used streptavidin-coated AuNPs to provide impedimetric signal amplification for detecting DNA hybridization events. The probe oligomer was adsorbed on a graphite/epoxy composite electrode and the impedance measurement was performed using a ferrocyanide/ferricyanide redox marker. The coating with streptavidin favoured the rapid formation of conjugates with biotinylated target DNA hybrid with a limit of detection 11.8 pM.⁷²⁸

DNA sensing has likewise been performed using AuNP-DNA conjugates on GCEs using methylene blue (MB) as an electroactive label and differential pulse voltammetry (DPV). The resulting system enhanced the response signal during immobilization and hybridization by increasing the density of redox active sites.⁷²⁹ Fang and coworkers have immobilized an oligonucleotide with a mercaptohexyl group at the 5'-phosphate end onto 16 nm AuNPs self-assembled on a cystamine-modified gold electrode. The modified electrode immobilized 10-fold greater quantities of ssDNA than planar gold electrodes.⁷³⁰

AuNPs can change the conductivity across a microelectrode gap, providing highly sensitive electronic detection of DNA hybridization.^{731,732} Mirkin and coworkers have reported an electronic DNA detection method where a short capture oligonucleotide was immobilized

between electrodes in a microelectrode array with 20 μm gaps. Using a three-component sandwich approach, hybridized target DNA and AuNPs functionalized with oligonucleotides were bound between the electrodes leads followed by silver deposition onto AuNPs to enhance conductivity (Figure 23). Using this method, a sensitivity of 500 fM has been achieved with a point mutation selectivity factor of $10^5:1$ in target DNA.⁷³² Following the same principle, Urban *et al.* have studied the changes of resistance across the microelectrode gap resulting from AuNP-labeled DNA in a parallel array readout system.⁷³³ Additionally Diessel and coworkers have further demonstrated the utility of this strategy for the detection of single-nucleotide polymorphism.⁷³⁴

The redox properties of AuNPs have been used as electrochemical labels for DNA detection. For example, Ozsoz *et al.* have developed a sandwich-type electrochemical genosensor where the labeled target was captured by probe strands immobilized onto a graphite electrode and hybridization detected by electrochemical gold oxidation.⁷³⁵ The response is enhanced due to the many oxidizable gold atoms in each nanoparticle label, with the detection limit as low as 0.78 fmol DNA for PCR amplicons. Similarly, another design was used to determine a specific binding event between *E. coli* ssDNA binding protein (SSB) and single-stranded oligonucleotides conjugated to AuNPs. SSB was adhered onto a SAM of single-stranded oligonucleotide modified AuNPs, and the resulting Au-tagged SSB was used as the hybridization label. Binding of Au tagged SSB to the probe was monitored through Au oxidation signal change, providing a detection limit of 2.17 pM target DNA.⁷³⁶ Willner *et al.* reported an amplified electrochemical DNA detection method using aggregation of AuNPs on electrodes.⁷³⁷ In their sensor, MB acts as a specific electrochemical indicator for the dsDNA aggregation of the AuNPs, with the AuNP assemblies facilitating the electrical communication of the intercalated MB with the electrodes with a detection limit of 0.1 pM for a 27-mer DNA. More recently, a new strategy for the label-free electrochemical DNA detection has been developed using an AuNP/poly(neutral red) modified electrode that transduces hybridization through current decrease, with a detection limit of 4.2 pM.⁷³⁸

In addition to DNA recognition, AuNP-DNA-modified electrodes have been used to study the interaction of DNA with small molecules. For example, a DNA-modified electrode was fabricated by self-assembling (3-Aminopropyl) trimethoxysilane and AuNPs and electrochemically immobilizing DNA onto ITO electrode. This DNA-modified electrode was used to detect the synthetic abortifacient, mifepristone with a detection limit of 200 nM.⁷³⁹ Likewise, interfacial interactions between immobilized DNA probes and DNA binding drugs were investigated using impedance spectroscopy. Use of AuNP functionalized substrates resulted in detection limits of 5 nM for nogalamycin, 10 nM for mythramycin, and 40 nM for netropsin, 15–40-fold lower compared to flat gold substrates.⁷⁴⁰ A norepinephrine biosensor was designed using an electrodeposited DNA membrane doped with AuNPs with a detection limit of 5 nM.⁷⁴¹

6.6 AuNP-based Electrochemical Immunosensors

Electrochemical immunosensors based on AuNPs enhance the electrochemical signal transduction of the binding event between antigen and antibody, providing a better surface for maintaining immunoreagent stability upon immobilization.⁷⁴²

6.6.1. Detection of Viral Surface Antigens & Others—Antibody immobilization onto AuNP-modified electrodes has been used to detect Hepatitis B virus surface antigen (HBsAg) with detection limits of 50 ng/L⁷⁴³ and 7.8 ng/mL.⁷⁴⁴ Similarly, HBsAg detection was performed by electrostatic adsorption of the corresponding antibody onto AuNP/tris(2,2-bipyridyl)cobalt (III) multilayer films,⁷⁴⁵ AuNPs entrapped on polyvinyl butyral/nafion film coated PtE surface,⁷⁴⁶ cysteamine and AuNP modified gold electrodes.⁷⁴⁷ Other studies have used a nanoporous gold electrode with HRP labeled secondary antibody–AuNPs bioconjugates,⁷⁴⁸ by self-assembling AuNPs to a thiol-containing sol-gel network and assembling hepatitis B surface antibody on to the surface of AuNPs^{749,750} and by immobilizing hepatitis B surface antibody on a platinum disk electrode based on an AuNP/nafion/gelatin matrix.⁷⁵¹ An alternate strategy involving AuNPs and HRP modified gold electrode was used to build an amperometric immunosensor for HBsAg (Figure 24). The sensor was comparable to a BSA-blocked immunosensor in terms of linearity and sensitivity and detected HBsAg as low as 0.85 ng/mL.⁷⁵² Recently, a label-free amperometric immunosensor based on chitosan-branched ferrocene (CS-Fc) and AuNPs was developed to detect HBsAg. The decrease of amperometric signal corresponding to specific antigen-antibody binding was proportional to HBsAg concentration with a detection limit 0.016 ng/mL.⁷⁵³ A copper-enhanced AuNP tag provided improved electrochemical performance for detecting HBsAg with a detection limit of 87 pg/mL.⁷⁵⁴

Diphtheria antigen was detected through diphtheria antibody immobilization on PtE modified with AuNPs^{755,756} and silica/silver/AuNPs⁷⁵⁷ in polyvinyl butyral matrices. A modified approach using a mixture of AuNPs and silica nanoparticles provided higher sensitivity, better reproducibility, and long-term stability of the system.⁷⁵⁸ A label-free amperometric immunosensor based on multi-layer assembly of polymerized *o*-phenylenediamine and AuNPs was used to detect Japanese B encephalitis vaccine with a detection limit of 6×10^{-9} log pfu/mL (pfu/mL is plaque forming unit).⁷⁵⁹

Electrochemical AuNP-based immunosensors have been used to detect a wide array of small molecule analytes, including carcinogenic substances (Aflatoxin B1,^{760,761} Ochratoxin A,^{762,763} naphthalene,⁷⁶⁴ paraoxon),⁷⁶⁵ herbicides (atrazine,^{766,767} picloram⁷⁶⁸), and hormones (human chorionic gonadotrophin hormone (pregnancy test marker),^{769–774} progesterone,^{775,776} phytohormone abscisic acid,⁷⁷⁷ 17 β -estradiol,^{778,779} human growth hormone⁷⁸⁰). Furthermore, detection of different proteins such as transferrin,^{781,782} human serum albumin,^{783,784} thrombin,⁷⁸⁵ hemoglobin,⁷⁸⁶ protein A,⁷⁸⁷ and apolipoprotein A-I⁷⁸⁸ has also been successfully achieved.

6.6.2. Detection of Biomarkers for Cancer and Other Disease States— α -Fetoprotein (AFP) is a tumor-marker for metastatic cancer. Several groups have used AuNP-based immunosensors to detect AFP by immobilizing AFP antibodies onto AuNP-decorated thionine/nafion membranes,^{789,790} through electro-deposition of AuNPs and prussian blue on ITO electrode,⁷⁹¹ using carbon paste electrode constructed with an ionic liquid and AuNPs,⁷⁹² with AFP-antibody functionalized AuNPs,⁷⁹³ using chitosan-AuNP composite film on a GCE,⁷⁹⁴ using films of MWCNT/DNA/thionine/AuNPs,⁷⁹⁵ using 1,1'-bis-(2-mercapto)-4,4'-bipyridinium dibromide functionalized AuNPs onto GCE,⁷⁹⁶ and by immobilizing AFP-antigen onto GCE modified with AuNPs and a CNT doped chitosan

film.⁷⁹⁷ AuNPs and enzyme amplification have been applied to develop an immunosensor to detect AFP based microelectrodes and microwells systems fabricated by SU-8 photoresist on silicon wafer with a detection limit of 5 ng/mL.⁷⁹⁸

Another biomarker, carcinoma antigen 125 (CA125) was electrochemically detected by immobilizing anti-CA125 on a thionine and AuNP-modified carbon paste electrode.⁷⁹⁹ Anti-CA125 was later immobilized on AuNPs stabilized with a cellulose acetate membrane on a GCE surface. Using *o*-phenylenediamine and H₂O₂ as enzyme substrates, the sensor provided a competitive immunoassay format to detect CA125, with HRP-labeled CA125 antibody as a tracer.⁸⁰⁰ Similarly, various antigens were successfully detected by several groups using AuNP-based immunosensors, e.g. carbohydrate antigen 19-9,⁸⁰¹ carbohydrate antigen 125,⁸⁰² prostate-specific antigen,^{803–807} and mammary cancer 15-3 antigen.⁸⁰⁸

A wide range of additional biomarkers have been detected besides cancer biomarkers, including cholera toxin,⁸⁰⁹ interleukin-6,^{810–812} vascular endothelial growth factors,⁸¹³ Annexin II and MUC5AC antigens,⁸¹⁴ *Schistosoma japonicum* antigen,^{815,816} *Salmonella typhi* antigen,^{817,818} foodborne pathogen *Escherichia coli* O157:H7,⁸¹⁹ osteoprotegerin,⁸²⁰ protein markers for acute myocardial infarction (AMI) e.g. myoglobin, cardiac troponin complex and the MB isoform of the enzyme creatine kinase,⁸²¹ dust mite allergen Der f2,⁸²² carcinoembryonic antigen (CEA),^{823–837} etc. Recently, Ho *et al.* have reported an AuNP-based electrochemical sandwich immunosensor for α -Enolase (ENO1) antigen, a potential diagnostic marker for lung cancer. The immunosensor operates through physisorption of anti-ENO1 monoclonal antibody on polyethylene glycol-modified disposable screen-printed electrodes followed by using anti-ENO1-tagged AuNP congregate bioprobes as electrochemical signal probes (Figure 25) with a detection limit as low as 11.9 fg (equivalent to 5 μ L of a 2.38 pg/mL solution).⁸³⁸ Recently, Ju and coworkers have developed a disposable reagentless electrochemical immunoassay array for multianalyte determination by immobilizing AuNPs modified with HRP-labeled antibodies on screen printed electrodes. Chitosan/sol-gel was used to trap the corresponding antigens of the analytes from the sample solutions.^{839,840} Upon formation of immunocomplex, the direct electrochemical signal of the HRP decreased due to increasing steric blocking.

6.6.3. Detection of Immunoglobulins—Immunoglobulins are important biomarkers for a wide variety of disease states. Numerous examples of determining human immunoglobulin G (IgG)^{841–856} as well as immunoglobulin E (IgE)⁸⁵⁷ via AuNP-based electrochemical immunosensors can be found in literature. For example, Velev and Kaler designed a conductivity immunoassay system that used silver metallization to enhance sensitivity.⁸⁵⁸ Mao *et al.* have reported an electrochemical method based on copper precipitation onto AuNP tags to detect human IgG and anodic stripping voltammetry (ASV) reaching a detection limit of 0.5 ng/mL.⁸⁵⁹ Pioneering work using AuNPs as electrochemical labels for voltammetric detection of proteins were performed by Costa-García *et al.*^{860,861} and Limoges *et al.*⁸⁶² For example, Limoges and coworkers reported an electrochemical immunoassay for IgG using AuNP-labeled antibodies and ASV. In this approach, the AuNP-labeled antibody forms sandwich complexes with the goat IgG target and the immobilized antibody. After removal of the unbound labeled antibody, AuNPs were dissolved in an acidic bromine-bromide solution to release gold ions that were electrochemically detected,

providing an IgG detection limit of 3 pM,⁸⁶² competitive with ELISA. Likewise, human IgG has been detected by ASV using cyclic accumulation of AuNPs. In this sensor, the probe antibody in the sandwich complexes is labeled with dethiobiotin and avidin-AuNPs. The alternating treatment of the system with biotin solution and avidin-AuNPs resulted in cyclic accumulation of AuNPs. The detection limit of this method was 0.1 ng/mL of human IgG.⁸⁶³ Recently, Merkoçi and coworkers reported an electrocatalytic silver-enhanced metalloimmunoassay using AuNPs as labels and microparamagnetic beads (MBs) as platforms for primary antibody immobilization to detect human IgG with a very low detection limit of 23 fg/mL (Figure 26).⁸⁶⁴ Finally, based on the catalytic effect of AuNPs on the electroreduction of silver ions, Huang and coworkers have reported the sensitivity enhancement for an electrochemical immunoassay by the autocatalytic deposition of Au³⁺ onto AuNPs. By coupling the autocatalytic deposition with square-wave stripping voltammetry, the model analyte rabbit IgG could be determined quantitatively with a detection limit 1.6 fM.⁸⁶⁵

The rather analogous mouse IgG was identified with a detection limit of 1 ng/mL using a reagentless amperometric immunosensor based on AuNPs on a nafion modified GCE with 3,3',5,5'-tetramethylbenzidine (TMB) as redox mediator.⁸⁶⁶ A polymer-membrane based potentiometric IgG sensing method using silver enlargement of AuNPs tracers was reported by Chumbimuni-Torres *et al.* to detect mouse IgG with a detection limit of ~12.5 pmol in the 50 μ L sample.⁸⁶⁷ A novel DNA-free ultrasensitive sandwich-type heterogeneous electrochemical immunosensor using AuNP nanocatalyst labels was reported by Das *et al.*⁸⁶⁸ As illustrated in Figure 27a partially ferrocenyltethered dendrimer (Fc-D) was immobilized to the ITO electrode by covalent bonding between dendrimer amines and carboxylic acids of a phosphonate self-assembled monolayer. Unreacted amines of Fc-D were modified with biotin groups to allow the specific binding of streptavidin. Then, biotinylated antibodies were immobilized to the streptavidin-modified ITO electrode. An IgG-nanocatalyst conjugate was also prepared via direct adsorption of IgG on 10 nm AuNPs. Mouse IgG and prostate specific antigen (PSA) were chosen as target analytes (Figure 27b).⁸⁶⁸ The signal amplification was achieved by the catalytic reduction of *p*-nitrophenol (NP) to *p*-aminophenol (AP) using gold AuNP catalyst labels as well as through the NaBH₄ mediated chemical reduction of *p*-quinone imine (QI). This DNA-free method can detect 1 fg/mL of PSA, comparable to that of the bio-barcode assay.⁸⁶⁹ An extension of this model using magnetic beads for easy magnetic separation and immunoreactions leads to greater signal amplification by AuNPs, detecting mouse IgG as low as 7 aM using CV and 0.7 aM using DPV measurements.⁸⁷⁰

7. AuNP-based Surface Plasmon Resonance Sensors

The interaction of light at the surface of the noble metal film excites surface electromagnetic waves and sets them to resonate with incident light wave, resulting in the absorption of the light. This phenomenon is known as surface plasmon resonance (SPR)^{871,872} and depends on the refractive index of the interfacial region. Metal nanoparticles such as gold^{227,873–875} and silver^{876,877} exhibit localized surface plasmon resonance (LSPR) at specific incident wavelengths, generating strong light scattering and the appearance of intense surface plasmon absorption bands. The intensity and the frequency of the absorption band is a

characteristic of the particular metal nanoparticles and highly dependent on their size, shape as well as the surrounding environment.^{878–882} Using this phenomenon many LSPR-based chemical and biological sensors have been developed.^{14,309,883–895} Although numerous biosensors have been developed using silver nanoparticles^{896–903} we will focus on AuNP based sensors.^{894,904–915}

7.1. Sensors based on Change in LSPR Absorption of AuNPs

The general principle behind LSPR-based sensors is the wavelength shift in the LSPR spectrum arising from local dielectric changes caused by analyte adsorption. LSPR assays have been conducted both in solution phase^{916–918} and on surfaces coated with nanoparticle monolayers.^{919–922} In examples of the former, absorption maxima of LSPR was red-shifted when AuNPs functionalized with monoclonal antibodies interacted with analytes.^{923,924} Moreover, the wavelength shift was found to be proportional to the amount of ligands.⁹²⁴

Most AuNP-based SPR sensors, however, have been fabricated by immobilizing nanoparticles onto surface.^{925,926} The introduction of AuNPs onto the sensing surface provides an effective way to increase the sensitivity of SPR sensors owing to the high dielectric constants of AuNPs and the electromagnetic coupling between AuNPs and the metal film on the surface.⁹²⁷ For example, a gold film-coated chip was used to detect dopamine in nanomolar concentration by immobilizing an MIP gel with embedded AuNPs.⁹²⁸ Various substrates such as quartz, optical fibers, ITO glass, sol-gel matrix, etc. have been used for supports for AuNPs, allowing the detection of numerous analytes such as human serum albumin,⁹²⁹ BSA,^{930,931} human IgG,⁹³² streptavidin,⁹³³ interleukin-1 β ,⁹³⁴ propanethiol,⁹³⁵ etc. Recently, AuNPs encapsulated by hydroxyl/thiol-functionalized fourth generation PAMAM dendrimer were immobilized onto maleimide terminated SAMs to detect insulin.⁹³⁶ The resulting AuNP modified dendrimer surface provided high stability and enhanced sensitivity with a detection limit of 0.5 pM. The sensor was further testified by analyzing human serum samples from normal and diabetic patients with good correlation to standard methods.⁹³⁶

The aggregation of AuNPs leads to an alteration in surface absorption band that gives rise to a visible color change. Exploiting this principle, Mirkin *et al.* have developed a colorimetric sensor for DNA hybridization assay using oligonucleotide functionalized AuNPs both in dispersions as well as on surface (**See Section 4.4**). Other SPR based sensors using aggregation of AuNPs have been reported to detect proteins (via antigen-antibody or biotin streptavidin interaction),^{354,937,938} lectin,^{331,338} etc.

7.2. AuNP-mediated SPR Signal Amplification

AuNPs have been used to enhance the signals of the propagating SPR spectroscopic signals to increase sensor sensitivity.^{939–943} The signal amplification was explained by the electronic coupling interaction of the propagating surface plasmons with localized surface plasmons of AuNPs^{944,945} and depends on various factors such as size, shape, and the distance from the metal generating SPR.^{946,947}

7.2.1. Sensing of Proteins—Protein sensing through antigen-antibody interaction can be detected exploiting AuNP-amplified SPR phenomena. For example, Natan *et al.* have reported an AuNP-enhanced SPR immunosensing system using either antigen or secondary antibody functionalized AuNPs as signal enhancers.⁹⁰⁴ In an example of this sandwich strategy, a gold film coated with γ -chain and F_c specific monoclonal goat antihuman IgG (α -h-IgG(F_c)) generates a small plasmon shift upon addition of human IgG and the second free antibody. The plasmon shift, however, increases 28-fold times compared to an unamplified assay when the secondary free antibody is replaced by an electrostatic conjugate between AuNPs and α -h-IgG(F_c). Using this method picomolar detection of human IgG has been achieved. Similarly, several competitive and sandwich immunoassays have been developed using AuNP-enhanced SPR signals to detect human tissue inhibitor of metalloproteinases-2,⁹⁴⁸ anti-glutamic acid decarboxylase antibody,⁹⁴⁹ allergen,⁹⁵⁰ TNT,⁹⁵¹ human IgE,⁹⁵² and testosterone.⁹⁵³ The sensitivity of these assays can be enhanced using fluorescence-labeled antibodies decorated with AuNPs, leading to the technique called localized surface plasmon resonance coupled fluorescence fiber optic sensor.^{954–957}

7.2.2. Sensing of Oligonucleotides—The sensitivity of oligonucleotide detection can be improved by using AuNP-amplified SPR.^{958,959} Keating *et al.* have developed a sandwich approach where 12-mer oligonucleotides were first linked covalently onto a gold substrate followed by hybridization of one half of the target DNA molecules. Then, a sequence complementary to the other half of the target was added with or without tagging of AuNPs. The AuNP-tagged surface demonstrated a 10-fold increase in angle shift concomitant with a 1000-fold improvement in sensitivity and a ~ 10 pM detection limit for the target 24-mer oligonucleotide.⁹⁶⁰ For example, Zhou *et al.* have shown that an intermediate carboxylated dextran layer between gold film and the immobilized DNA molecules effectively eliminates the nonspecific adsorption of oligonucleotide functionalized AuNPs, resulting femtomolar level of detection for 39-mer DNA (Figure 28).⁹⁶¹ In a representative study, real time multicolor DNA detection has been achieved exploiting AuNP-amplified diffraction, where ssDNA-modified AuNPs and micropatterned chemoresponsive diffraction gratings were used to interrogate simultaneously at multiple laser wavelengths.⁹⁶²

7.3. Sensors based on AuNP Plasmon Resonance Scattering

In addition to changes in LSPR absorption, the plasmon resonance scattering phenomena of AuNPs provides a useful tool for sensor design.^{197,963} The plasmon scattering of 36 nm diameter AuNPs is 10–100 times stronger than dyes or quantum dots. Exploiting this nanoscale phenomena, several groups have developed immunoassays to detect human IgG,⁹⁶⁴ kanamycin,⁹⁶⁵ and lysozyme in human urine.⁹⁶⁶ For example, Ren and coworkers have developed a highly selective and sensitive homogeneous immunoassay and DNA hybridization assay using plasmon scattering of single AuNP probe. The sandwich immunoassay was used to detect cancer biomarkers such as CEA, AFP in femtomolar range, and aptamer recognition for thrombin as low as 2.72 pM.⁹⁶⁷ Recently, Ling *et al.* have reported an LSPR light scattering sensor for Ag^+ with unmodified AuNPs exploiting the specific recognition property of Ag^+ with a cytosine-cytosine mismatch base pair. The addition of Ag^+ removes the oligonucleotide from the AuNP surface causing aggregation

concomitant with dramatic increment of LSPR scattering intensity. The LSPR light scattering intensity was proportional to concentration of Ag^+ , with a limit of detection of 62 nM.⁹⁶⁸ El Sayed *et al.* have demonstrated a biosensor technique using SPR scattering images and SPR absorption spectra from anti-EGFR functionalized AuNPs for the diagnosis of oral epithelial cancer cells *in vitro*.⁹⁶⁹ The anti-EGFR functionalized AuNPs bind 600% stronger to oral malignant cells HOC 313 clone 8 and HSC 3 than normal cell HaCaT, resulting in a sharper SPR absorption band with a red shift (Figure 29).

8. Surface Enhanced Raman Scattering (SERS)-based Sensing

The physical phenomenon behind the Raman spectroscopy is the inelastic scattering of photons by a molecule having quantized vibrational level/signature.⁹⁷⁰ Raman scattering is sensitive to different vibrational modes and consequently can provide a “fingerprint” of the target molecules.⁹⁷¹ However, the direct application of this technique in sensitive detection and identification of analyte molecules is severely restricted owing to the low efficiency of inelastic photon scattering by molecules leading to a weak signal.⁹⁷² The inherent limitation of low scattering intensity arises from the fact that the Raman scattering cross-sections for molecules are usually small, typically 10^{-30} – 10^{-25} $\text{cm}^2/\text{molecule}$, 10 to 15 orders of magnitude smaller than that of fluorescence cross section. In the presence of plasmonic nanoparticles or rough metal surfaces, however, the Raman scattering intensity from a molecule can be enhanced by up to 10^{14} order of magnitudes.^{973–977} This phenomenon has been attributed to a local electromagnetic field enhancement induced by the plasmon resonance of surfaces and is called surface enhanced Raman scattering (SERS).^{978–981} The field enhancement is dependent on the size, shape, orientation, and aggregation of the nanoparticle. The large enhancement in detectable signal coupled with the unique molecular fingerprints generated has made SERS a powerful tool for the multiplex detection of analytes, with the ability to achieve a detection of single molecule level.^{976,977}

8.1. Detection of Small Organic Molecules

AuNPs have been utilized for the SERS based detection of small organic molecules such as explosives.^{982–985} For example, Ray *et al.* have used AuNPs modified with cysteine as label-free SERS probe for highly selective and sensitive recognition of TNT.⁹⁸² Cysteine modified AuNPs undergo aggregation in the presence of TNT due to the formation of donor-acceptor Meisenheimer complex between TNT and cysteine. The resulting ‘hot spots’ for enhancement of the Raman signal provided a sensitivity of 2 pM level. Kneipp *et al.* have shown that SERS nanosensor made from AuNP nanoaggregates and 4-mercaptobenzoic acid attached as a reporter can be used for monitoring changes in local pH of the cellular compartments of living cells.⁹⁸⁶

8.2. Detection of Oligonucleotides

Mirkin *et al.* have utilized AuNP probes labeled with oligonucleotides and Raman-active dyes for the SERS-based multiplexed detection of DNA and RNA targets (Figure 30).⁹⁸⁷ To detect the presence of specific target DNA strands, a three-component sandwich assay in a microarray format was used. For the assay, dye-labeled AuNP probes were captured by the target oligonucleotide strands, followed by silver enhancement, generating detectable SERS

signals exclusively from the Raman dyes immobilized on the particles, with a limit of detection of 20 fM. More importantly, this method was able to discriminate single nucleotide polymorphisms relating to six different viruses. Irudayaraj *et al.* have incorporated non-fluorescent Raman tags onto DNA-conjugated AuNP (~30 nm) probes for the SERS detection of DNA.⁹⁸⁸ In their system, the surface coverage of the Raman tags on the AuNP surface has been modulated to control the intensity of Raman signal from the probes. Simultaneous identification of upto eight probes with a detection limit of ~100 nM without further metal enhancement was achieved. A DNA sensor using SERS from AuNP aggregates formed via DNA photoligation has been described by Maenosono *et al.*⁹⁸⁹ In their system, SERS signals arise after hybridization from the Raman-active molecules present in the NP aggregates. Liu *et al.* have reported a sequence-specific DNA detection using SERS spectroscopic fingerprint from thiol-oligonucleotide-modified ZnO/Au nanocomposite probes.⁹⁹⁰ Nie *et al.* have developed a SERS beacons using DNA conjugated AuNP probe.⁹⁹¹ Signals from this AuNP-based SERS beacons can be turned on and off by biomolecular binding and dissociation events. Using both distance dependent SERS enhancement of the isolated AuNPs and the “hot spots” created by two conjugated AuNPs, Hu *et al.* have developed a novel nano-junction based biosensor for the detection of sub-attomolar HIV-1 DNA.⁹⁹² Johnson *et al.* have demonstrated an indirect capture model assay for SERS-based detection of DNA using AuNPs.⁹⁹³ SERS based approach-utilizing AuNP probes for identifying and quantifying multiple gene segments extracted from cells has been described by Irudayaraj *et al.*⁹⁹⁴ Multiple AuNP-on-wire systems as a SERS sensing platform for viral DNA have been developed by Kang and coworkers.⁹⁹⁵ Their particle-on-wire sensor provided SERS signals only in the presence of target DNA, leading to the detection of DNA concentration ranging from 10 pM to 10 nM. Raman dye labeled AuNP probes have also been applied for SERS based *in vivo* and *in vitro* imaging.^{996–1001}

8.3. Detection of Proteins

AuNPs have been widely used in SERS based immunoassays of proteins.^{1002–1009} For example, Grubisha *et al.* reported an immunoassay using 30 nm AuNPs functionalized with a monolayer of an intrinsically strong Raman scatterer (5-thiol-2-nitrobenzoate) followed by a layer of covalently linked antibodies.¹⁰⁰⁴ In this system, a sandwich assay format based on monoclonal antibodies has been used for the detection of free PSA. The sensitivity from this system has been drastically enhanced due to their unique sensor design, which not only minimizes the separation between label and particle surface but also maximizes the number of labels on each particle. The detection limit of this immunoassay was ~1 pg mL⁻¹ in human serum. Kim *et al.* have demonstrated a label-free detection system for avidin via avidin-mediated self-assembly between biotinylated Au nanowires and biotinylated AuNPs. The avidin induced self-assembly process created ‘hot spots’ between the nanowire and AuNPs that strongly enhanced the Raman signal.¹⁰¹⁰ An aptasensor based on the formation of SERS ‘hot spots’ between nanowires and AuNPs has also been used to detect human α -thrombin in serum.¹⁰¹¹ Hu *et al.* have used AuNPs functionalized with thrombin specific aptamer for the detection of thrombin.¹⁰¹² Their electrostatic interaction based assay approach provided a detection limit of 20 pM. Mirkin *et al.* have used AuNPs functionalized with either protein ligands or antibodies and Raman dyes to perform multiplexed screening of protein-small molecule interactions and protein-protein interactions in a microarray

format.¹⁰¹³ Reich *et al.* have employed DNA-bridged AuNP assemblies for the detection of protein-DNA interactions via SERS.¹⁰¹⁴ Self-assembly of peptide functionalized AuNPs has been used for the SERS based detection of proteases.¹⁰¹⁵ Wang *et al.* demonstrated a microarray approach based on SERS for the detection of peptide-protein or protein-antibody interactions.¹⁰¹⁶ A SERS-based assay technique was developed by Gu *et al.* to detect the activity of alkaline phosphatase enzyme at ultralow concentrations.¹⁰¹⁷ SERS based rapid screening of pathogenic bacteria has also been achieved utilizing AuNPs.^{1018,1019}

9. AuNPs in Quartz Crystal Microbalance-based Sensing

Quartz crystal microbalances (QCM) are ultrasensitive piezoelectric devices that use frequency changes on a quartz crystal resonator to monitor changes in mass arising from analyte binding. This technique has been widely used to sense chemical vapors, microorganisms, and DNA probes due to its high sensitivity and label-free detection.^{1020–1026} The incorporation of AuNPs into QCM-based sensing systems¹⁰²⁷ can enhance detection sensitivity by their high surface area and by serving as a “mass enhancer” by amplifying the frequency changes.¹⁰²⁸ On the small molecule front, AuNPs and AuNP-dendrimer composite behaving as sorptive materials have been utilized to detect chemical vapors.^{1029–1032}

9.1. Detection of Oligonucleotides

Several groups have reported QCM-based oligonucleotide sensors incorporating AuNPs.¹⁰³³ For example, Duan and coworkers have shown the introduction of AuNPs greatly enhances the immobilization capacity and the detection limit for oligonucleotide sensing using QCM.¹⁰³⁴ In their findings, the immobilization of ~12 nm diameter AuNPs onto a gold coated QCM resulted in easier attachment of thiol containing ssDNA, resulting in higher sensitivity upon addition of target oligonucleotides. Sandwich-based approaches using ssDNA-modified AuNPs, can significantly improve the detection limit, where one end of the target oligonucleotide hybridizes with the immobilized ssDNA (recognition element) while the other end hybridizes with AuNPs (mass enhancer).^{1035–1043} It should be noted, however, the nonspecific adsorption of AuNPs to the gold film of QCM should be avoided to prevent the overestimation of signal amplification.¹⁰⁴⁴ On the other hand, catalytic deposition of gold films onto amplifier AuNPs has been proved to enhance the sensitivity of the QCM approach for DNA detection, and a detection limit of 1 fM has been achieved.¹⁰⁴⁵ Microcantilever-based DNA sensors are a parallel method that monitors mass changes on much smaller platforms. The sensor element, however, in comparison to QCM, is at least 100 times smaller, providing a high density sensor array for multiplexed detection. Using the sandwich approach together with AuNP-mediated amplification on a microcantilever, Dravid *et al.* obtained a detection limit of 23 pM for a 30-mer DNA.¹⁰⁴⁶

9.2. Detection of Proteins

Several sandwich type assays on QCM using AuNPs have been reported for immunosensing of proteins.^{1047–1052} For example, detection of streptavidin on a QCM has been achieved using AuNPs as a signal amplifier.¹⁰⁵³ The experimental set up involves the immobilization

of biotinylated BSA on the gold surface of the QCM electrode. Addition of streptavidin generates a small frequency change that is amplified by incubation with biotin functionalized AuNP providing a detection limit of 1 ng/mL. A similar approach has been described by Kim *et al.* to detect C-reactive protein.¹⁰⁵⁴ To attain further sensitivity Su *et al.* developed a QCM biosensor using primary AuNP-amplified sandwich immunoassay with silver enhancement technique. The AuNP-promoted silver reduction and the deposition of silver improved the detection of human IgG with two fold of magnitudes.¹⁰⁵⁵ Other QCM-based biosensors have also been reported for the detection of pathogens,^{1056–1058} antisperm antibody,¹⁰⁵⁹ human carcinoma cells,¹⁰⁶⁰ lectin,¹⁰⁶¹ and dengue virus¹⁰⁶² exploiting analogous AuNP-enhanced signal amplification.

10. AuNP-based Bio-Barcode Assays

A multiplexed and ultrasensitive detection for proteins and nucleic acids has been developed by Mirkin *et al.* using an AuNP-based bio-barcode assay to amplify the target molecules.^{16,1063,1064} The bio-barcode assay was first utilized for identifying PSA.⁸⁶⁹ As illustrated in Figure 31a, the target of interest PSA was captured by targeting antibodies immobilized on magnetic microparticles. An AuNP encoding double-stranded barcode DNAs and PSA targeting antibodies then bound with the magnetic microparticle. After magnetic separation of the complexes, thermal dehybridization of the barcode DNAs on AuNPs was carried out to afford the single-stranded free barcode DNA and the ssDNA encoded AuNPs. The free barcode ssDNAs were analyzed by using the PCR amplification to determine the presence of PSA, providing a limit of detection of 3 aM. When the ssDNA-encoded AuNP probes were analyzed by using chip-based hybridization followed by silver amplification, PSA was detected at 30 aM.⁸⁶⁹

Exploiting the same principle, an AuNP-based bio-barcode assay to detect DNA has also been reported.^{1065–1067} As shown in Figure 31b specific ssDNA replaced the antibodies on magnetic microparticle in the protein detection system. Upon complementary binding with the target DNA, both magnetic microparticle and bio-barcoded AuNPs form sandwich assemblies. The magnetic separation of the sandwich assemblies followed by thermal dehybridization released the free bar-code DNA for analysis. Scanometric detection of this method provides 500 zeptomolar sensitivity, comparable to many PCR-based approaches.¹⁰⁶⁶ The authors also demonstrated that the bio-barcoded amplification method can be used for identifying multiple DNA targets and bacterial genomic DNA.¹⁰⁶⁸

The bio-barcode assay has been applied to detect specific targets for many diseases.^{1069,1070} The bio-barcode approach has also been used to measure the concentration of amyloid- β -derived diffusible ligand (ADDL), a soluble pathogenic Alzheimer's disease marker in the cerebrospinal fluid (CSF).¹⁰⁷¹ In this work, the bio-barcode assay was used to detect ADDL in CSF at clinically relevant concentrations (< 1 pM) that were not detectable by conventional ELISA or blotting assay. Mirkin *et al.* also reported a bio-barcode assay for detecting human telomerase, a biomarker for cancer diagnosis.^{1072,1073} Recently, AuNP-based bio-barcode assay has been conducted to detect PSA in the serum of patients who have experienced radical prostatectomy for prostate cancer.¹⁰⁷⁴ The assay is ~ 300 times more sensitive than commercial immunoassays.

The AuNP-based bio-barcode assay has been employed for multiplexed detection of protein cancer markers by using a mixture of different bio-barcode AuNP probes.^{1075,1076} During the detection process, the released barcode DNA molecules can be specifically immobilized onto DNA functionalized surfaces followed by hybridization with ssDNA-AuNP and silver amplification. The multiplexed barcode assay can detect the target markers at low-femtomolar concentrations in serum.

An analogous fluorophore labeled bio-barcode amplification method simplifies the detection process of the previously reported bio-barcode AuNPs assay by eliminating the requirement for barcode sorting.¹⁰⁷⁷ Quantification of the assay is analyzed by measuring the fluorescence intensity of the released fluorophore-labeled barcode DNA. When the assay was tested with PSA, a detection limit of 300 aM was obtained without enzymatic amplification or microarray analysis. Wolff *et al.* have reported fluorescent DNA barcode-based assay for detecting avian influenza virus with PCR-like sensitivity.¹⁰⁷⁸

A colorimetric bio-barcode amplification assay has been developed by Groves *et al.* for the protein detection.^{1079,1080} In this system, the released barcode DNAs serve as a bridging agent for two ssDNA-functionalized AuNPs, inducing aggregation of the AuNPs and consequent red-to-blue color change to detect target molecules. The authors showed that cytokine, a biomarker for immunodeficiency-related diseases was detected upto 30 aM concentration, three orders of magnitude more sensitive than conventional cytokine detection assays.

11. Concluding Remarks

The physical properties and ease of synthesis and functionalization make AuNPs a versatile platform for chemical and biological sensors. The ease of functionalization provides facile attachment of both specific and selective recognition elements. The optoelectronic and physical properties of AuNPs then enable a diverse array of transduction processes. Advanced nanodiagnostic techniques have paved the way for affording easy, rapid, low-cost, and multiplexed identification of biomarkers. However, optimization of parameters for the sensing systems is still required to meet the demands of clinical diagnostics. In particular, the development of efficient sensors to detect analytes in complex biological fluids such as urine, serum, and blood remains a challenge. Additionally, efficient detection of disease often requires multiplex analysis, an issue where the ease of functionalization can enhance both the recognition process as well as provide building blocks for further miniaturization and hence an increased number of recognition elements.. Taken together, AuNPs provide an exceptional platform for the creation of nanosensors. As described in this review, there have been numerous sensor systems fashioned to date of both fundamental and clinical importance. The fundamental advantages of AuNPs have generated an exponential increase in their use in sensing that will continue to revolutionize the field of diagnostics for years to come.

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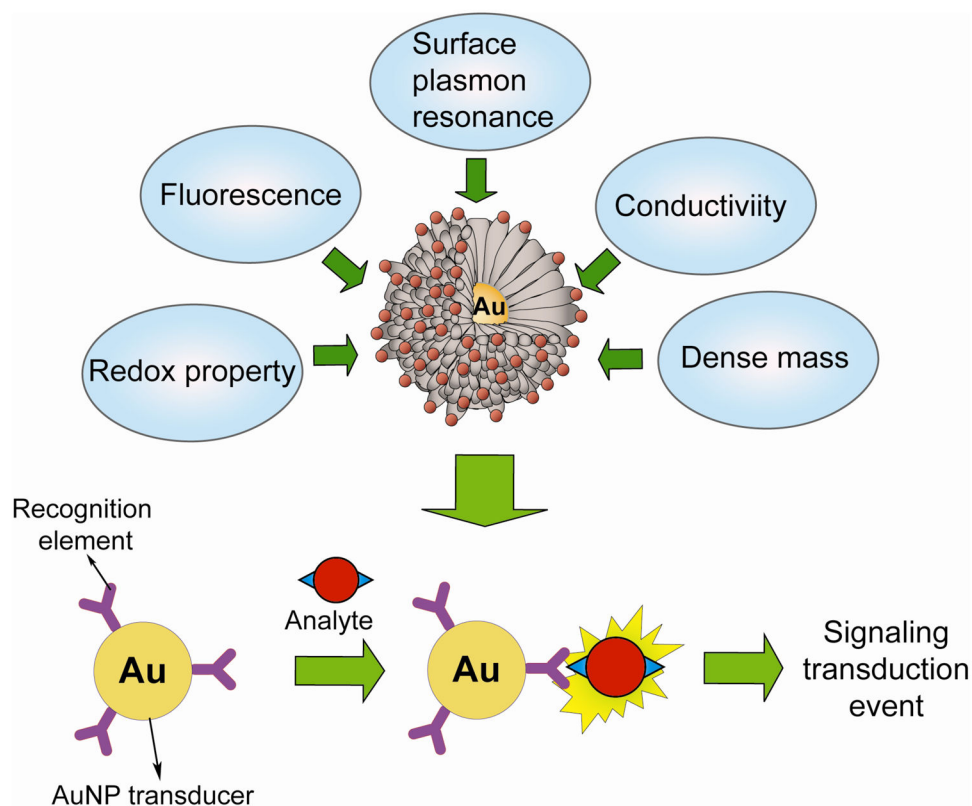


Figure 1. Physical properties of AuNPs and schematic illustration of an AuNP-based detection system.

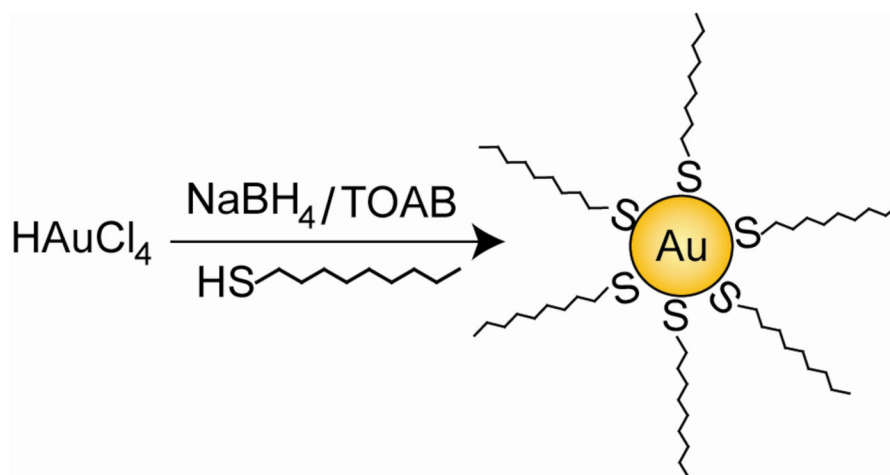


Figure 2. Brust-Schiffrin method for two-phase synthesis of AuNPs by reduction of gold salts in presence of external thiol ligands.

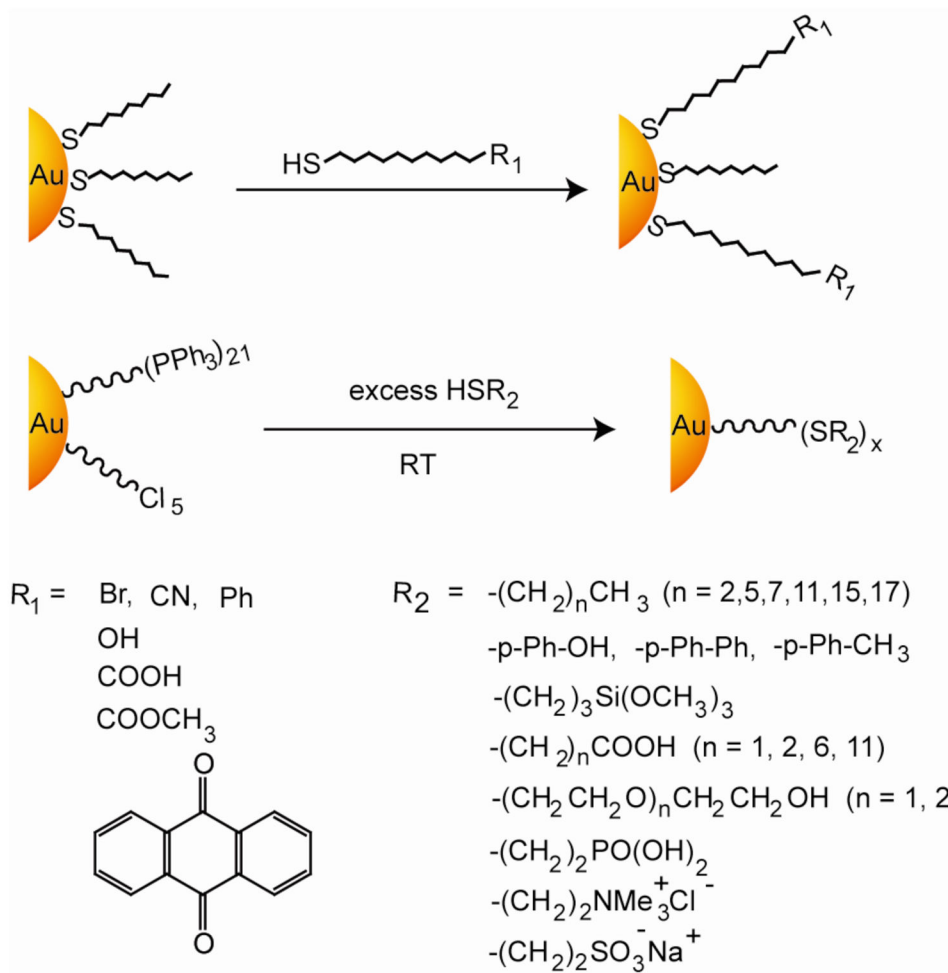


Figure 3. General scheme for place exchange reaction for alkanethiol-protected AuNPs using functionalized thiols, giving examples of particles that can be rapidly generated.

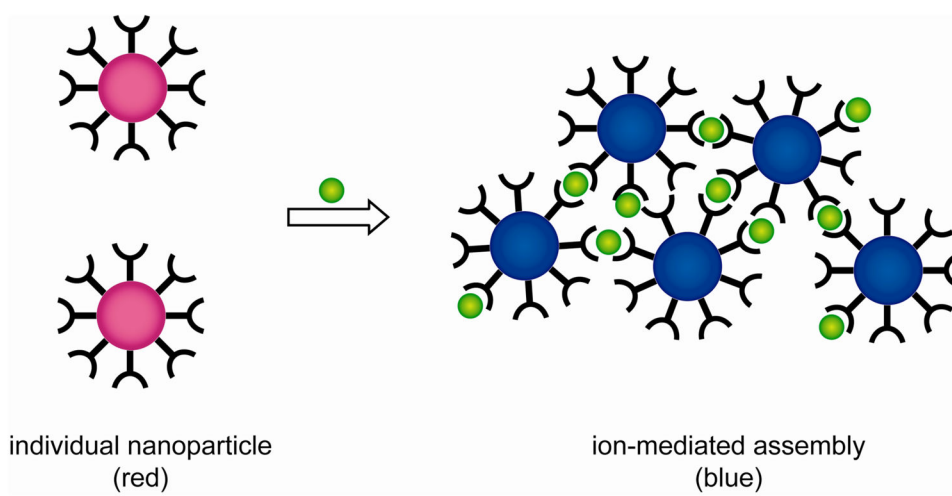


Figure 4. Schematic depiction of red-to-blue color colorimetric sensing of metal ions using chelating ligands.

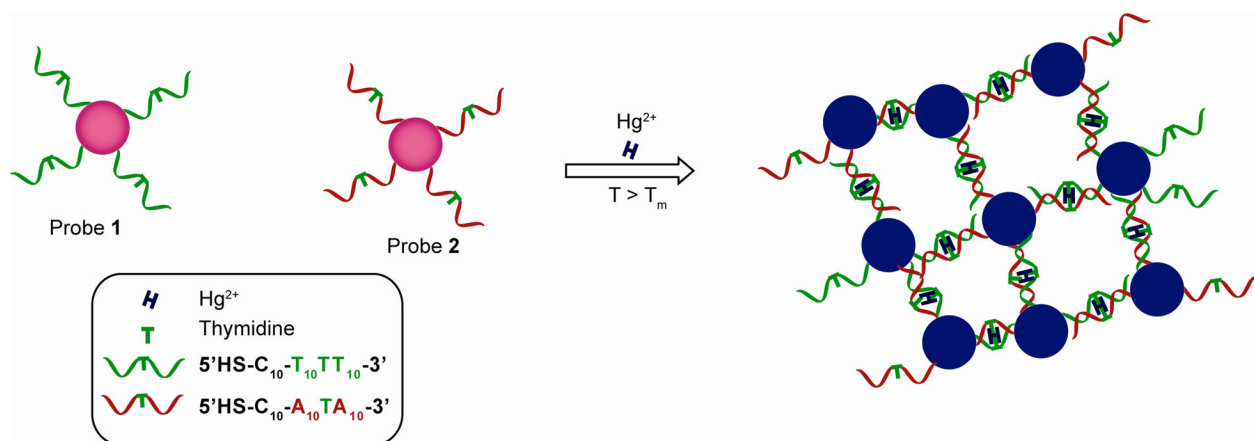


Figure 5. Colorimetric detection of Hg^{2+} using DNA functionalized AuNPs exploiting thymidine- Hg^{2+} -thymidine coordination chemistry.

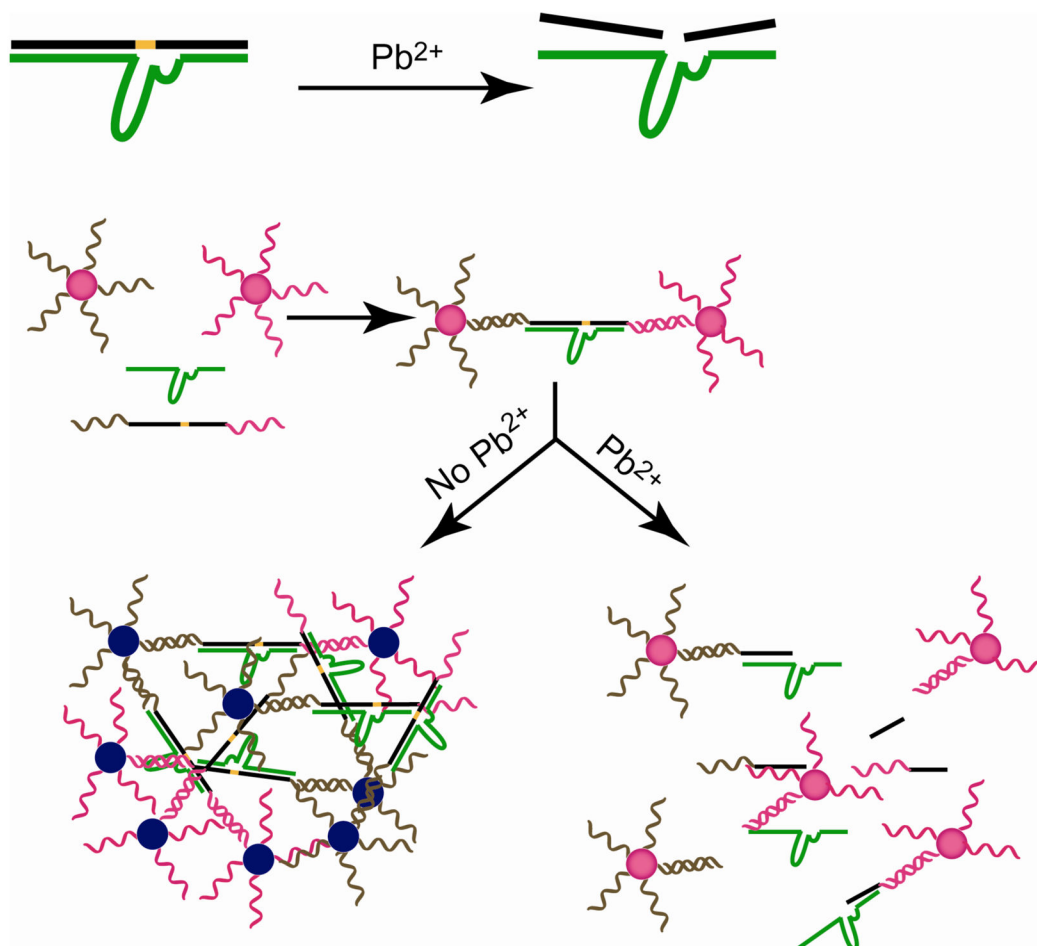


Figure 6. Pb^{2+} directed assembly of AuNPs by the DNazymes resulting in detection.

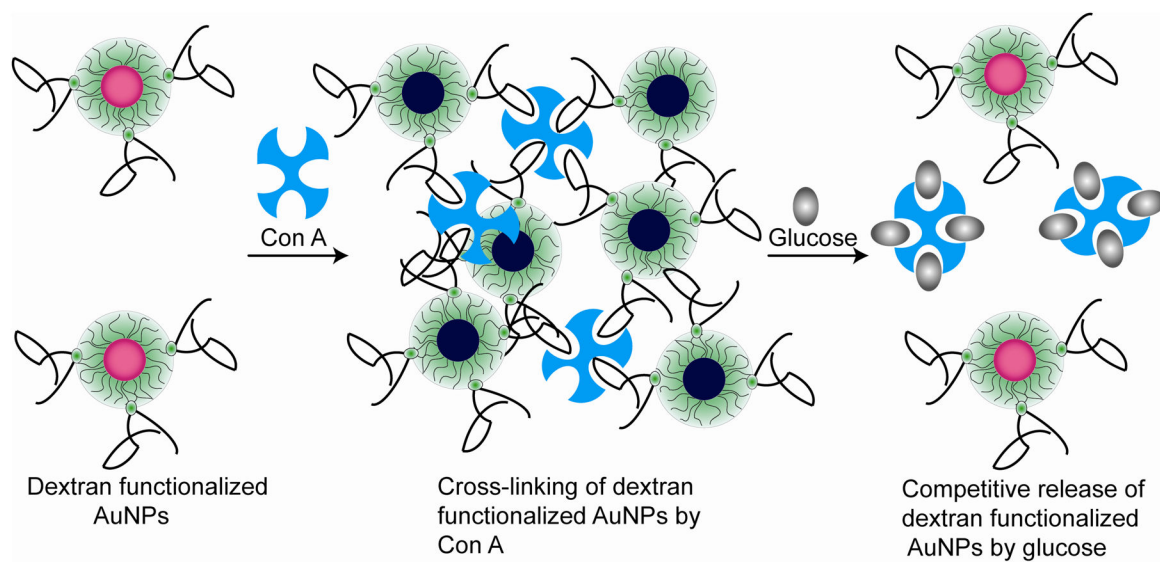


Figure 7.

Colorimetric glucose sensing via the dissociation of Con A-aggregated dextran coated AuNPs. The presence of Con A crosslinks dextran-coated AuNPs with concomitant blue-shift in SPR. The addition of glucose diminishes the Con A-AuNPs interaction releasing the individual dextran-coated AuNPs.

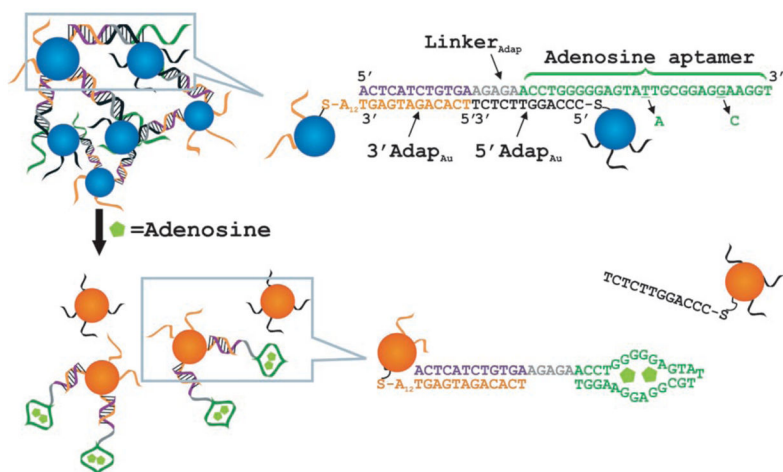


Figure 8. Schematic representation of colorimetric sensing of adenosine using aptamer linked AuNPs (left panel). The mutated linker with two mutations denoted by short black arrows was used as a control. Reprinted with permission from *Angew. Chem. Int. Ed.* (Ref 293). Copyright 2006 Wiley-VCH Verlag & Co. KGaA, Weinheim.

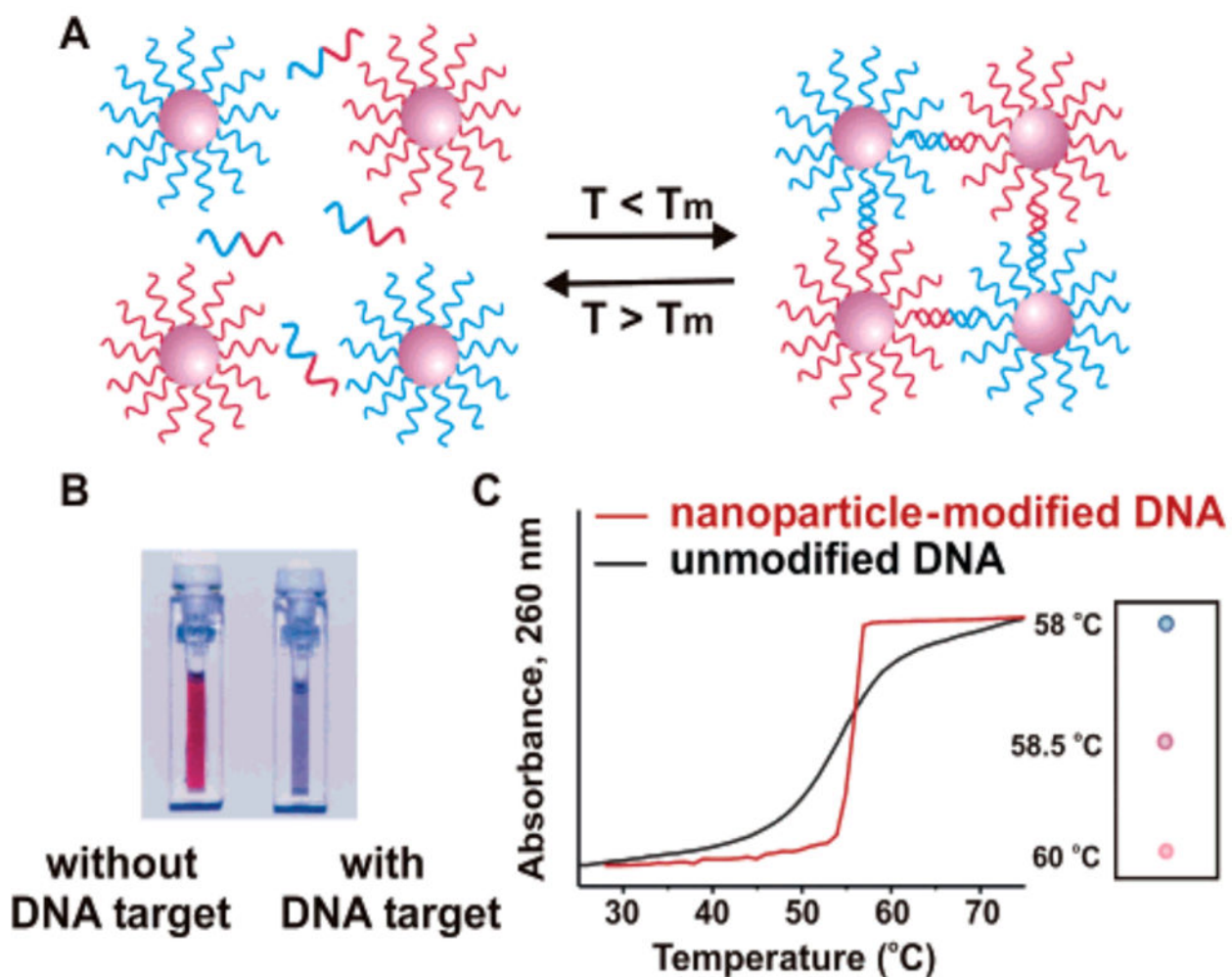


Figure 9. Aggregation of oligonucleotide AuNPs in presence of complementary target DNA (A), leading to change in color of solution from red to blue (B). Reprinted with permission from *Science* and *Chem. Rev.* (Ref 314 and Ref 16). Copyright 1997 American Association for the Advancement of Science and 2005 American Chemical Society.

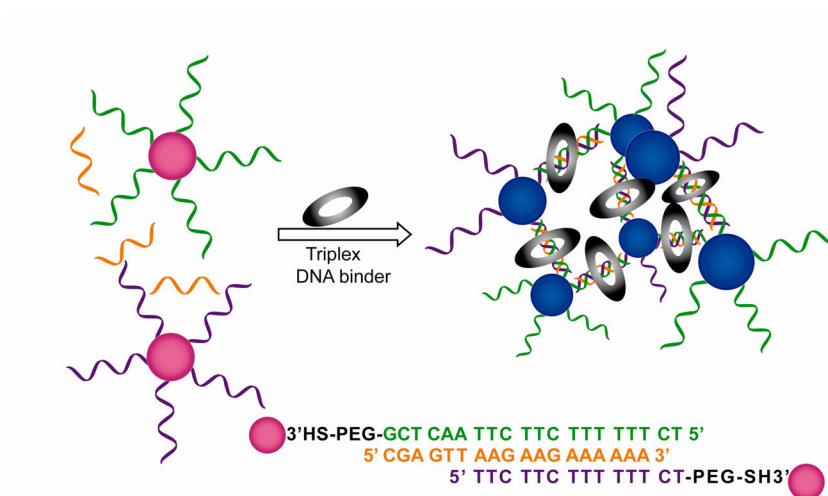


Figure 10. Schematic illustration of structure and color change of DNA functionalized AuNPs in presence of triplex DNA binders.

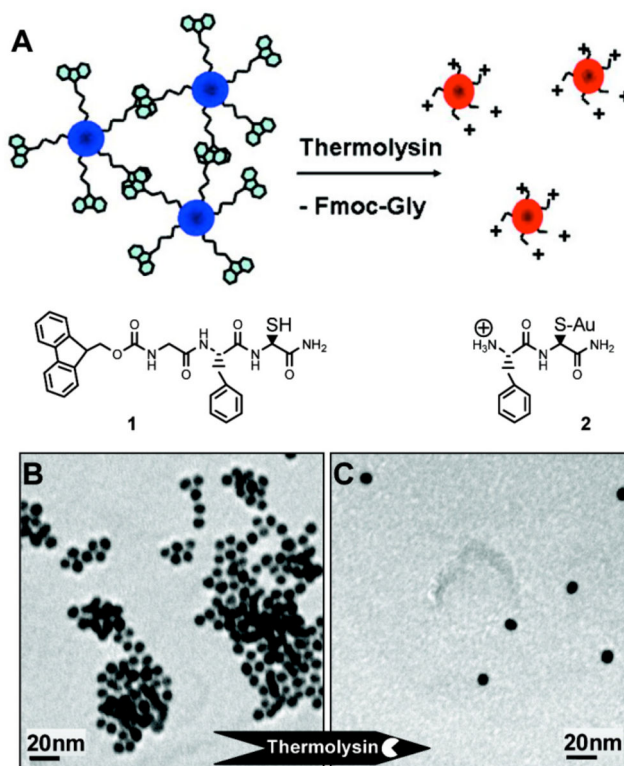


Figure 11. Schematic illustration of thermolysin triggered dispersion of AuNP assemblies (A), TEM images of AuNPs (functionalized with **1**) before (B) and after (C) addition of thermolysin and generation of **2**. Reprinted with permission from *J. Am. Chem. Soc.* (Ref 358). Copyright 2007 American Chemical Society.

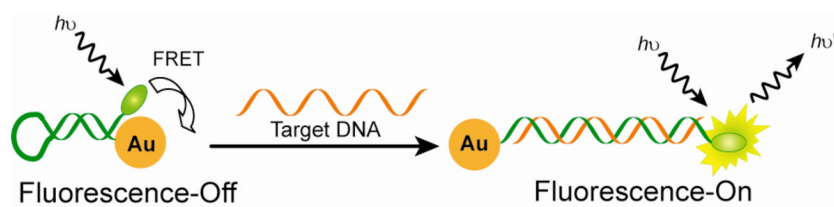


Figure 12. Schematic illustration of DNA detection, showing the conformational changes of dye-oligonucleotide-AuNP conjugates before and after hybridization with the target DNA.

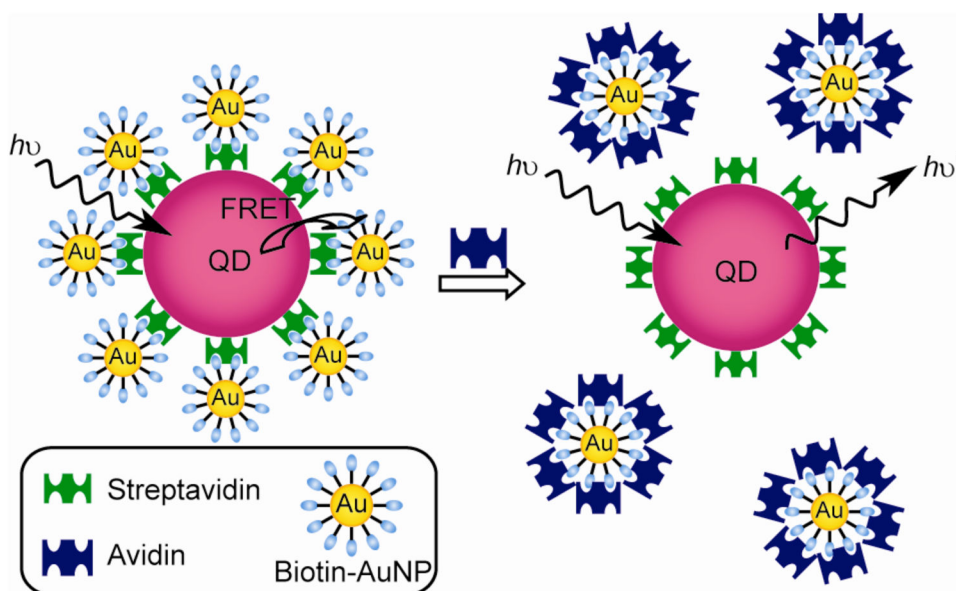


Figure 13. Competitive inhibition assay for the detection of avidin using QD-AuNP conjugates.

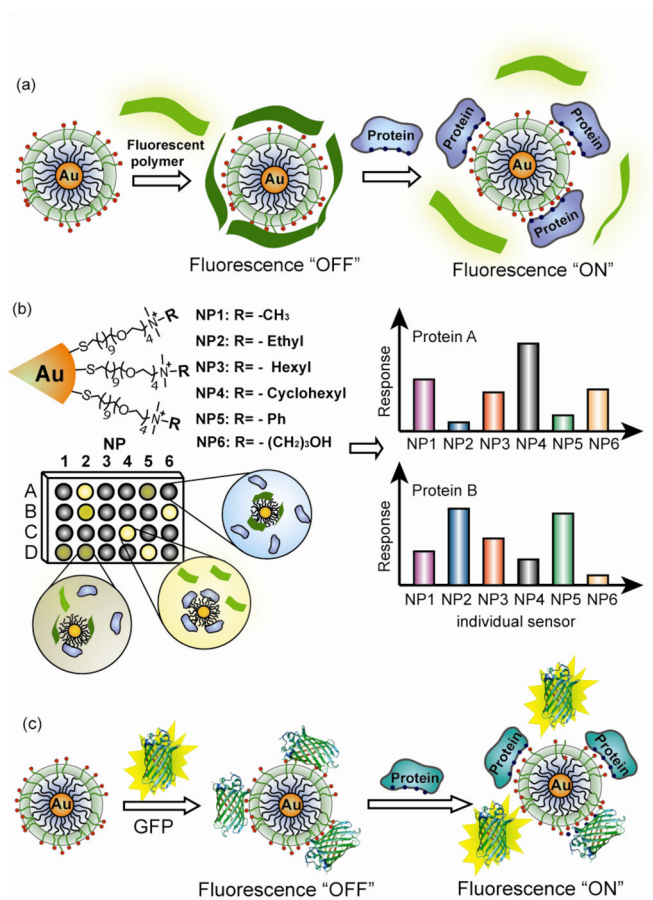


Figure 14. Schematic illustration of 'chemical nose' sensor array based on AuNP-fluorescent polymer/GFP conjugates. (a) The competitive binding between protein and quenched polymer-AuNP complexes leads to the restoration of fluorescence (b) The combination of an array of sensors generates fingerprint response patterns for individual proteins. (c) The competitive binding between protein and nanoparticle-GFP complexes leads to fluorescence light-up.

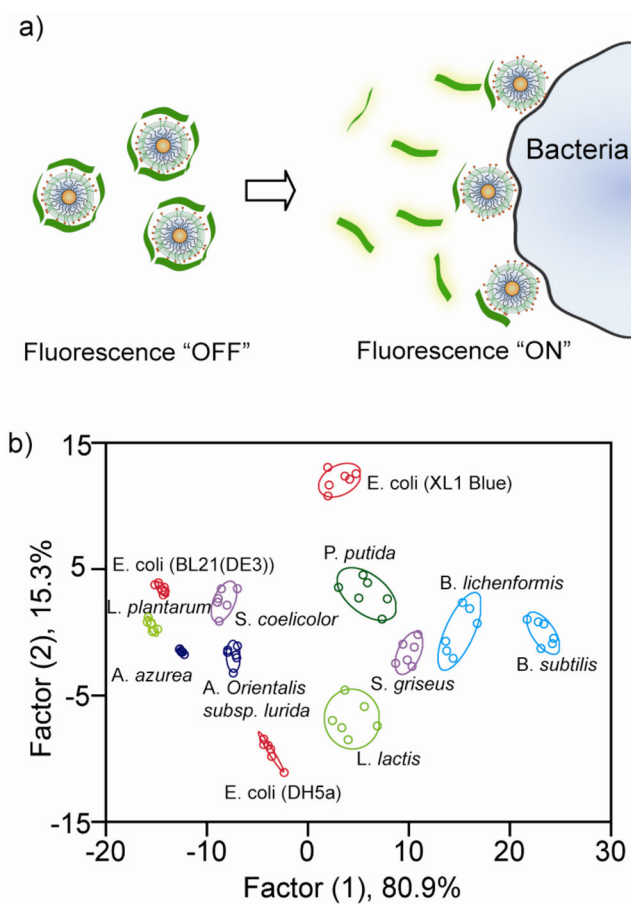


Figure 15.

Array-based sensing of bacteria. a) Displacement assay between bacteria and the AuNP-PPE complex. b) Canonical score plot for the first two factors of simplified fluorescence response patterns obtained with NP-PPE assembly arrays against bacteria (95% confidence ellipses shown). Reprinted with permission from *Angew. Chem. Int. Ed.* (Ref³⁹⁷). Copyright 2008 Wiley-VCH Verlag & Co. KGaA.

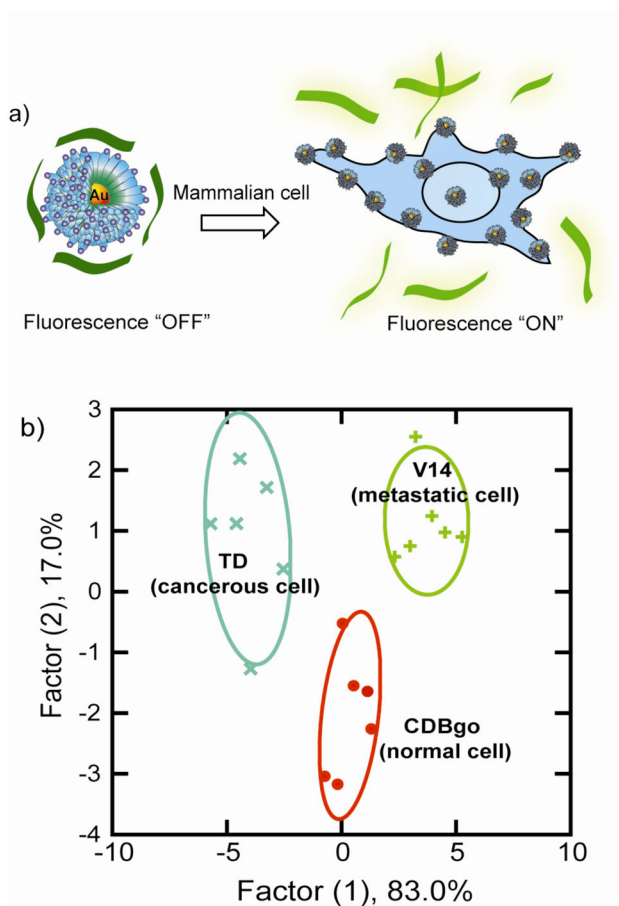


Figure 16.

a) Schematic depiction of the fluorophore-displacement cell detection array. Displacement of quenched fluorescent polymer by a cell with consequent restoration of polymer fluorescence. b) Canonical score plot for the first two factors of simplified fluorescence response patterns obtained with AuNP-conjugated polymer assembly arrays against different mammalian cell types. Reprinted with permission with permission from *Proc. Natl. Acad. Sci. U.S.A.* (Ref 398). Copyright 2009 National Academy of Sciences.

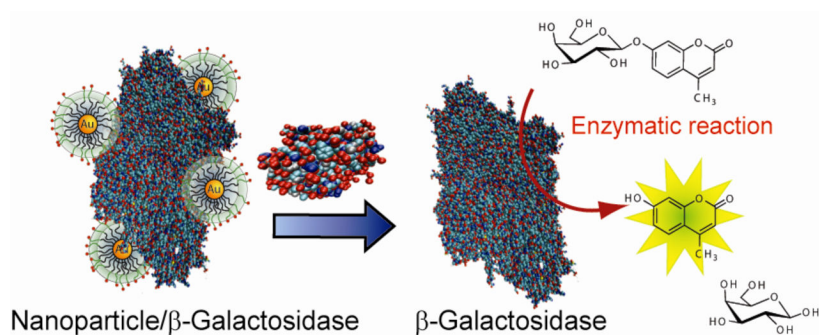


Figure 17.

A schematic representation of the sensor system comprised of β -galactosidase (β -Gal) and cationic AuNPs. β -Gal is displaced from the β -Gal/AuNP complex by protein analytes, restoring the catalytic activity of β -Gal towards the fluorogenic substrate 4-methylumbelliferyl- β -D-galactopyranoside, resulting in an amplified signal for detection. Reprinted with permission from *J. Am. Chem. Soc.* (Ref 401). Copyright 2010 American Chemical Society.

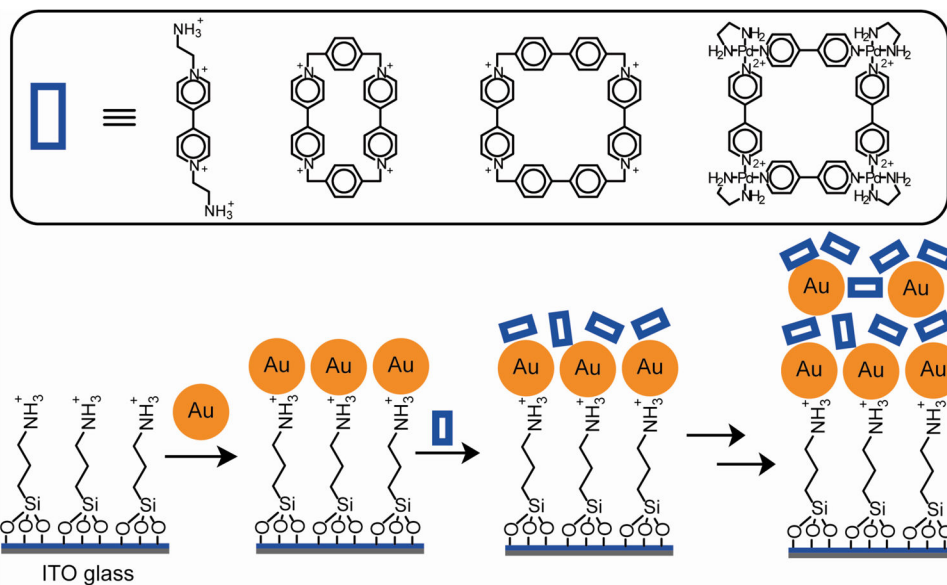


Figure 18. Electroactive multilayers formed by the simultaneous deposition of anionic AuNPs and oligocationic cyclophanes. The AuNPs provide excellent conductive surfaces, while the macrocycles serve as π -acceptors to bind with π -donor analytes (e.g. hydroquinone), generating electrochemical responses.

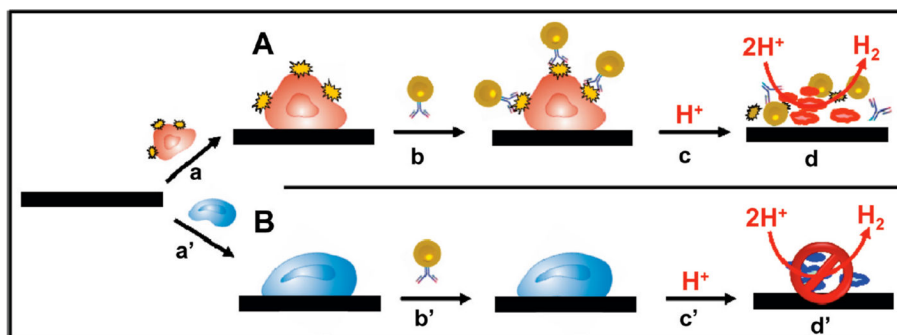


Figure 19. Specific identification of (A) Tumoral Cell Line (HMy2) expressing surface HLA-DR molecules compared to a (B) PC-3 Cell Line that is negative to this marker using AuNP-conjugated antibody coupled with an electrochemical sensor. The specific binding of AuNPs with tumor cells catalyses hydrogen evolution in the acidic environment, generating electrochemical responses. Reprinted with permission from *Anal. Chem.* (Ref 574). Copyright 2009 American Chemical Society.

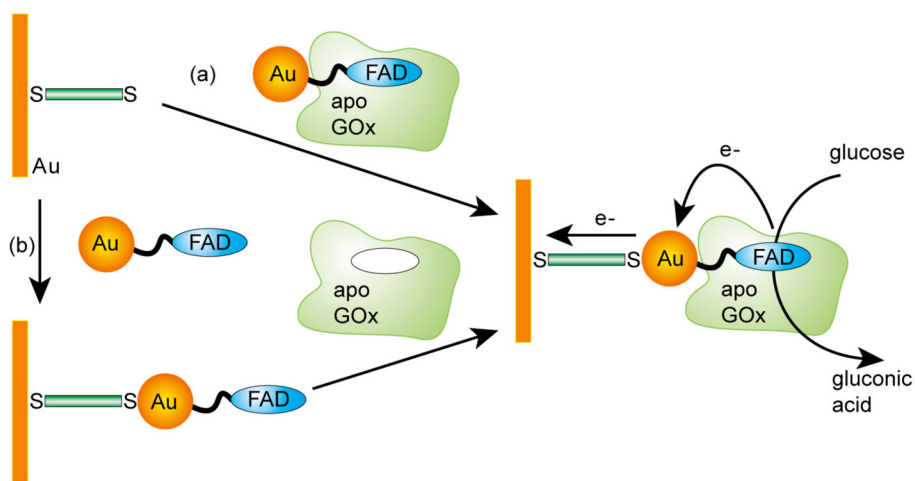


Figure 20.

Fabrication of GOx electrode by the reconstitution of GOx on a FAD-functionalized AuNP : (a) The adsorption of AuNP-reconstituted of apo-GOx to a dithiol monolayer assembled on a gold electrode and (b) the adsorption of FAD-AuNPs to a dithiol-modified gold electrode followed by the reconstitution of apo-GOx onto functional AuNPs. Reprinted with permission from *Science* (Ref 608). Copyright 2003 American Association for the Advancement of Science.

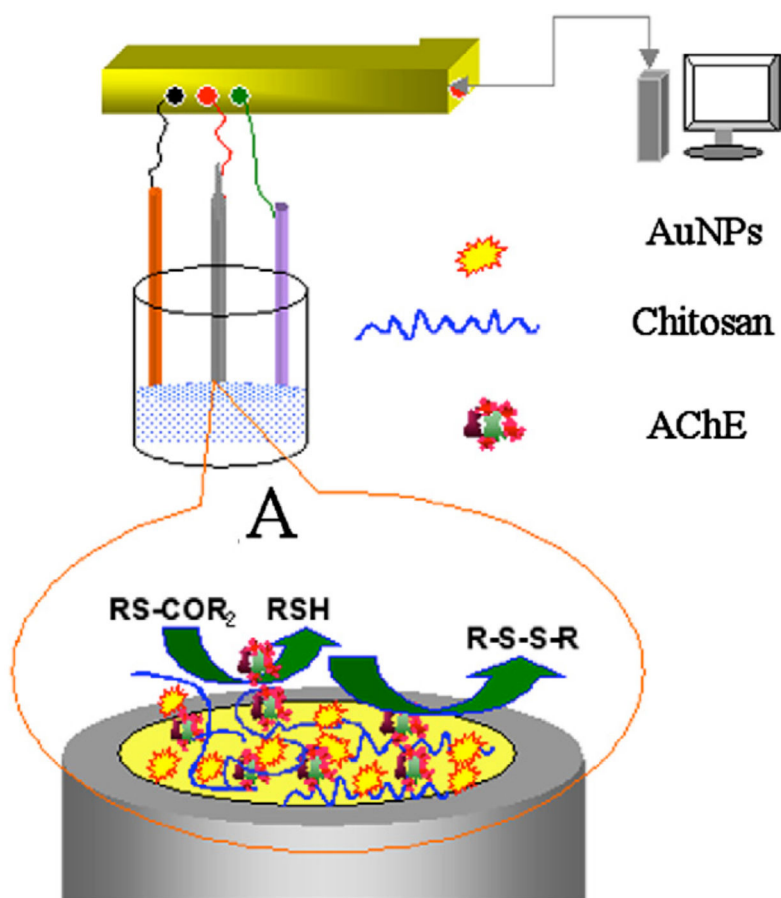


Figure 21. Acetylcholinesterase enzyme biosensor constructs using AuNPs/chitosan hydrogel matrices for the detection of pesticides. A) Megascopic interface of AChE/Chitosan–AuNP modified gold electrode. Reprinted with permission from *J. Electroanal. Chem.* (Ref 689). Copyright 2007 Elsevier B.V.

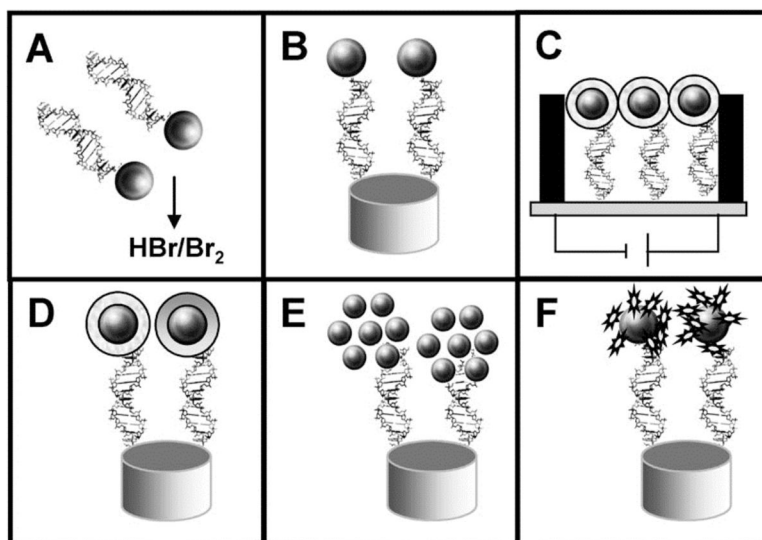
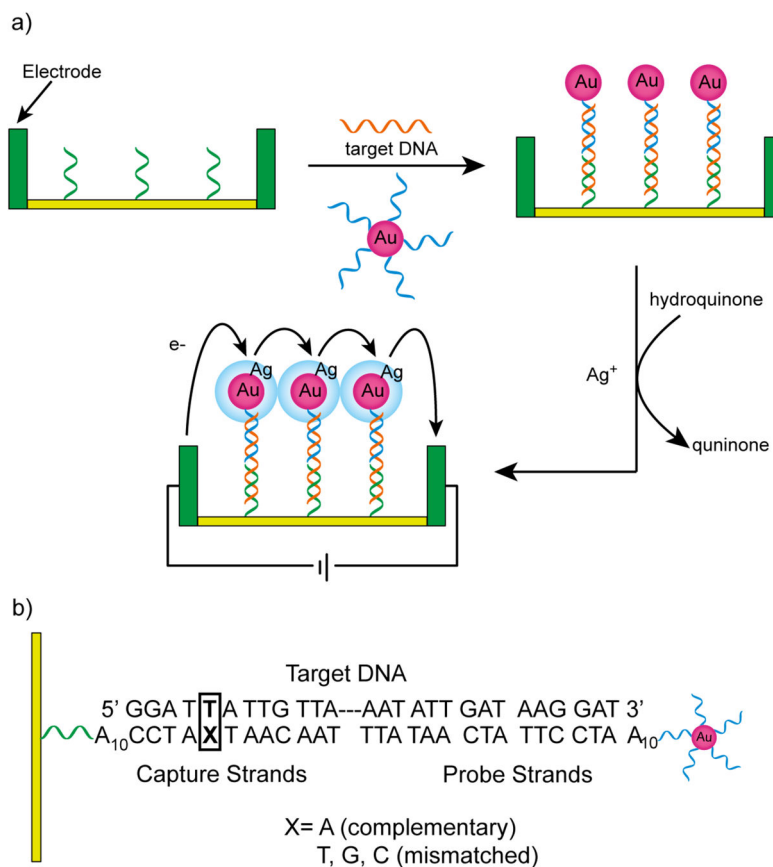


Figure 22.

Schematic procedure of the different strategies used for the integration of AuNPs into DNA sensing systems: (A) previous dissolving of AuNPs by using HBr/Br₂ mixture followed by Au(III) ions detection, (B) direct detection of AuNPs anchored onto the surface of the genosensor, (C) conductometric detection, (D) enhancement with silver or gold followed by detection, (E) AuNPs as carriers of other AuNPs, (F) AuNPs as carriers of other electroactive labels. Reprinted with permission from *Electroanalysis* (Ref 691). Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

**Figure 23.**

a) Schematic illustration of electrical detection of DNA based on “sandwich” hybridization with DNA functionalized AuNPs followed by silver enhancement. b) Sequences of capture, target, and probe DNA strands. Reproduced with permission from *Science* (Ref 732). Copyright 2002 American Association for the Advancement of Science.

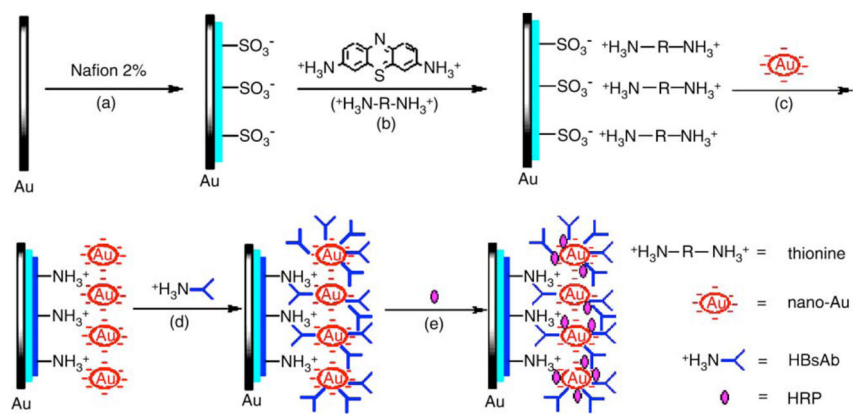


Figure 24. Schematic illustration of the stepwise immunosensor fabrication process to detect HBsAg: (a) formation of nafion monolayer; (b) adsorption of thionine; (c) formation of AuNP-monolayer; (d) HBsAb loading; (e) blocking with HRP. Reprinted with permission from *Anal. Chim. Acta* (Ref 752). Copyright 2005 Elsevier B.V.

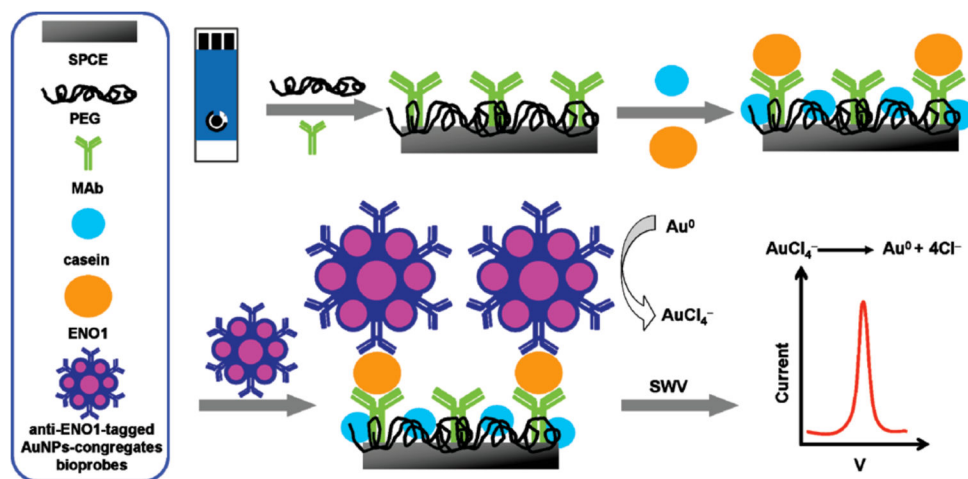


Figure 25. Schematic representation of the operation of the electrochemical immunosensor for the detection of ENO1. Reprinted with permission from *Anal. Chem.* (Ref 838). Copyright 2010 American Chemical Society.

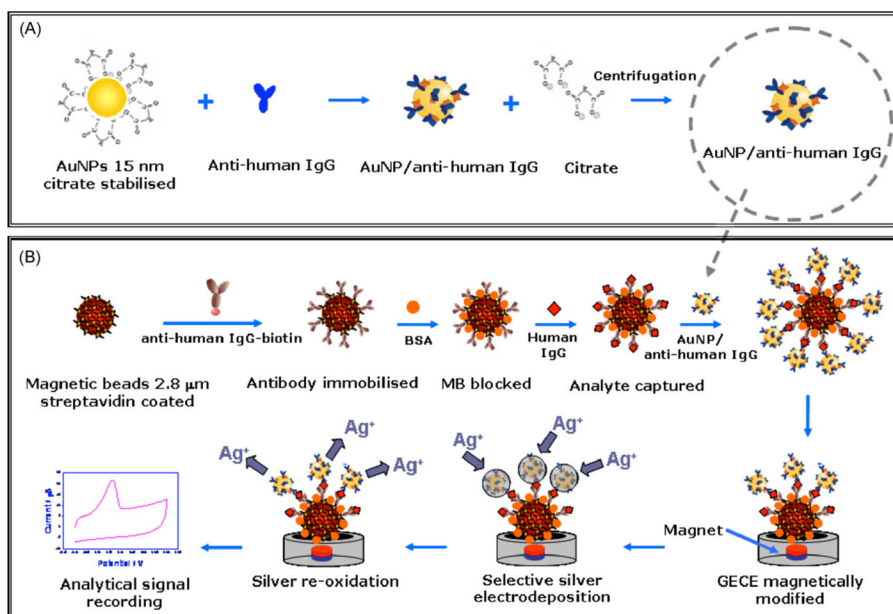


Figure 26.

(A) AuNP conjugation with anti-human IgG; (B) analytical procedure for the sandwich type assay and the obtaining of the analytical signal based on the catalytic effect of AuNPs on the silver electrodeposition. Reprinted with permission from *Biosens. Bioelectron.* (Ref ⁸⁶⁴). Copyright 2009 Elsevier B.V

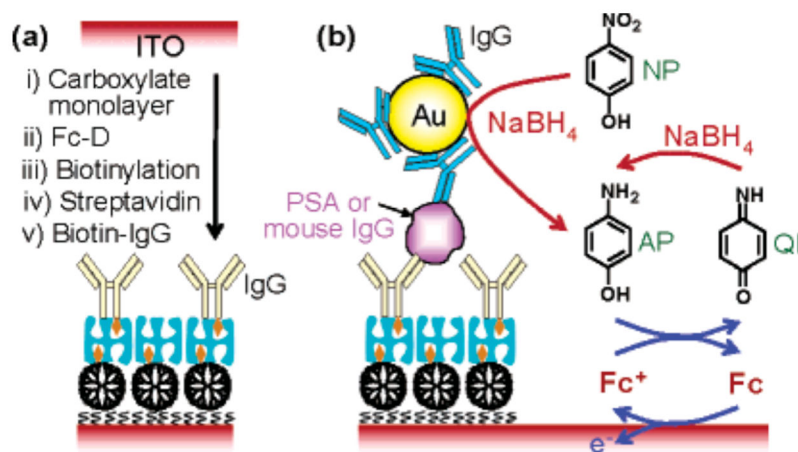


Figure 27.

(a) Schematic representation of the preparation of an immunosensing layer. (b) Schematic view of electrochemical detection of mouse IgG or PSA. Reprinted with permission from *J. Am. Chem. Soc.* (Ref 868). Copyright 2006 American Chemical Society.

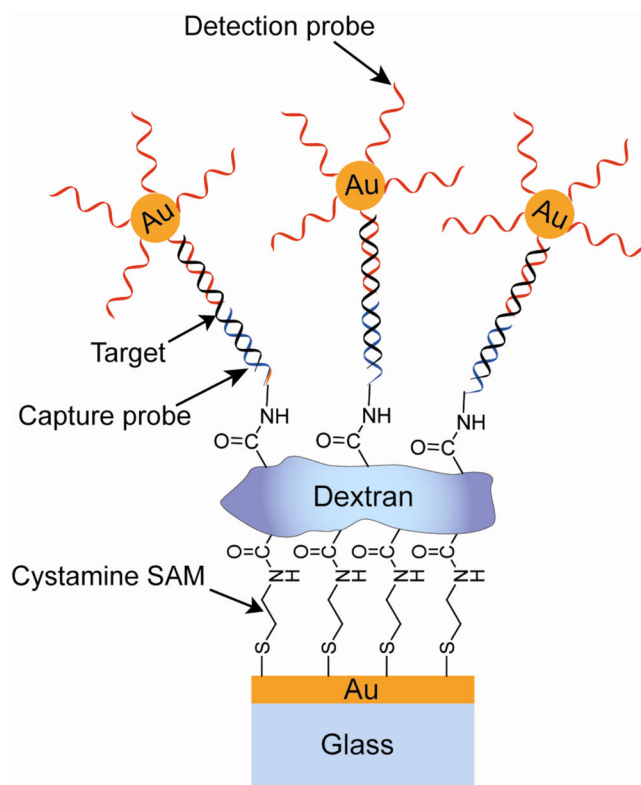


Figure 28. Schematic representation of sandwich DNA detection assay via AuNP-mediated SPR signal amplification. The SPR measurements were carried out by injecting the oligonucleotide functionalized AuNPs into the flow cell housing sensors covered with various duplexes or capture probes. The intermediate dextran layer reduces the nonspecific adsorption of AuNPs, improving detection sensitivity. Adapted from Ref 961.

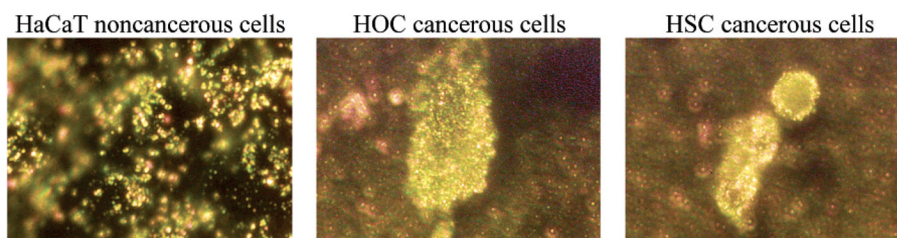


Figure 29. SPR light scattering images to distinguish between normal cells (left panel, HaCaT) and cancerous cells (middle & right panel, HOC and HSC) after incubation with anti-EGFR conjugated AuNPs. The anti-EGFR conjugated AuNPs bind specifically to the surface of cancer cells resulting in a sharper SPR band with a red shifted maxima. Reproduced with permission from *Nano Lett.* (Ref 969). Copyright 2005 American Chemical Society.

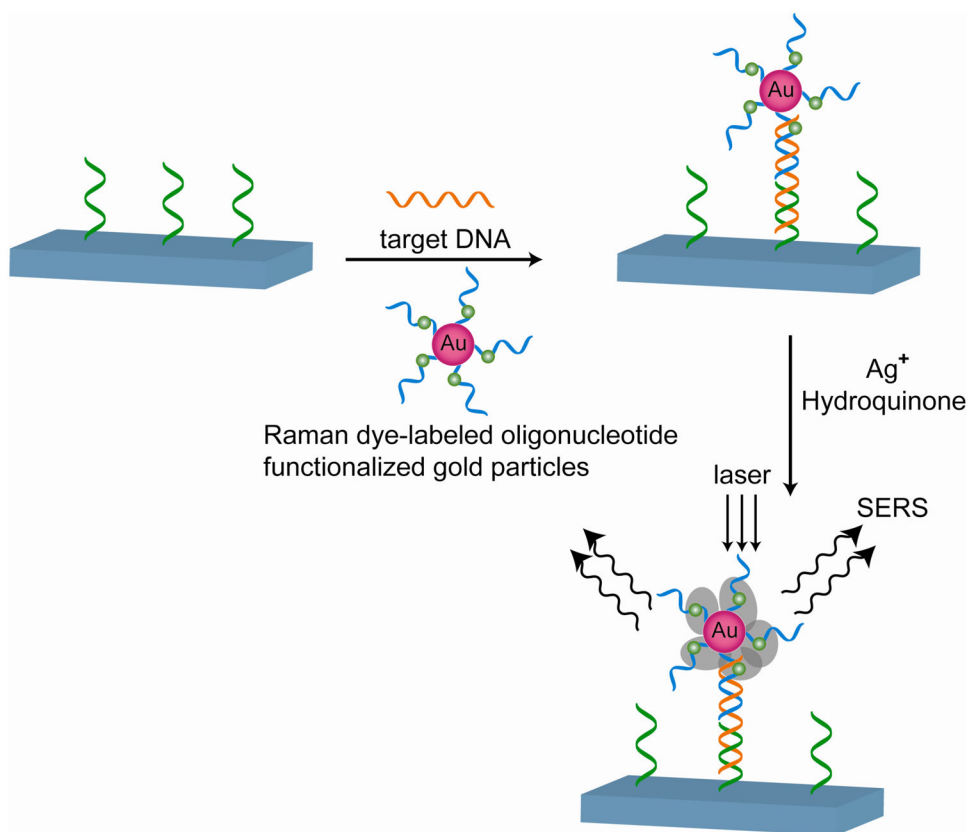


Figure 30. Schematic representation of three component sandwich assay for SERS-based oligonucleotide detection. Reproduced with permission from *Science* (Ref 987). Copyright 2002 American Association for the Advancement of Science.

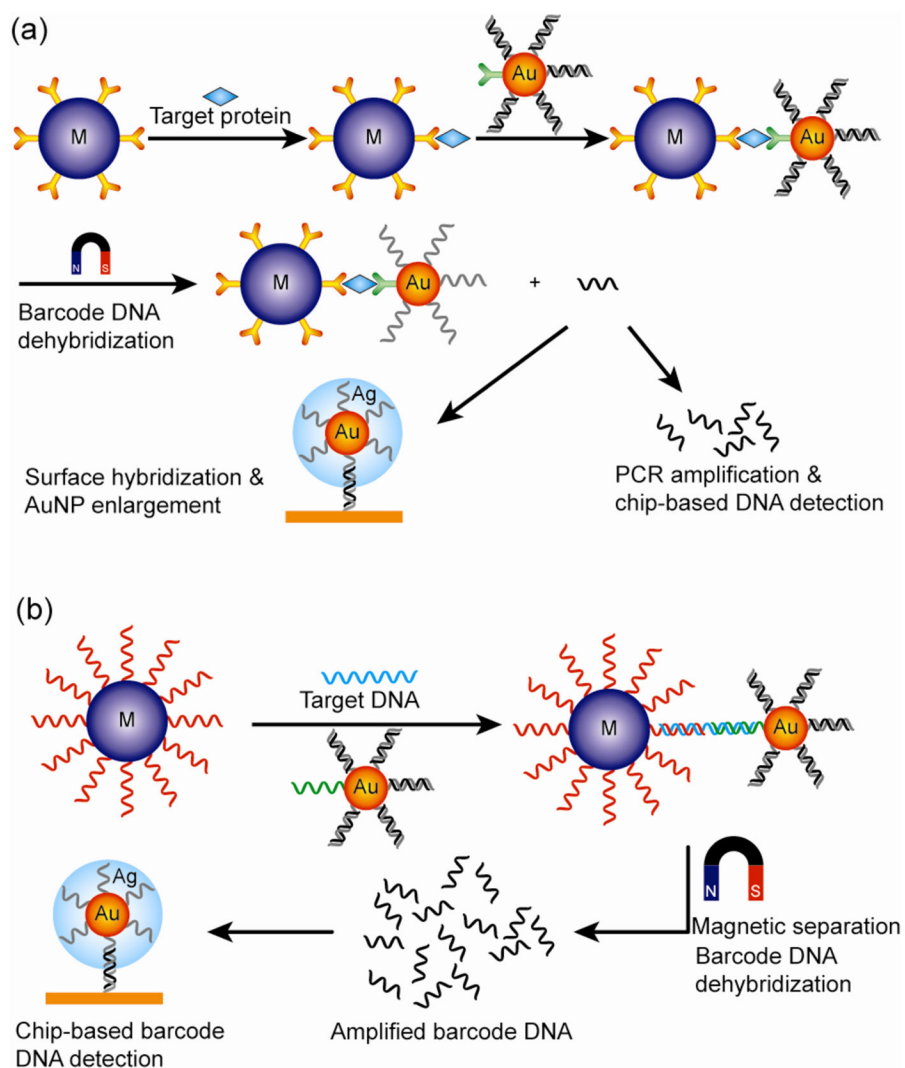


Figure 31.
AuNP-based bio-barcode assay of (a) proteins and (b) DNA