Review

Plasmon–Based Colorimetric Nanosensors for Ultrasensitive Molecular Diagnostics

Longhua Tang, and Jinghong Li

ACS Sens., **Just Accepted Manuscript** • Publication Date (Web): 06 Jun 2017

Plasmon–Based Colorimetric Nanosensors for Ultrasensitive Molecular Diagnostics

Longhua Tang,[a] Jinghong Li[b*]

[a] State Key Laboratory of Modern Optical Instrumentation, College of Optical Science and Engineering, Zhejiang University, Hangzhou 310027, China

[b] Department of Chemistry, Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Tsinghua University, Beijing 100084, China

*Corresponding E-mail jhli@mail.tsinghua.edu.cn (Prof. Jinghong Li)

Abstract

Colorimetric detection of target analytes with high specificity and sensitivity is of fundamental importance to clinical and personalized point-of-care diagnostics. Because of their extraordinary optical properties, plasmonic nanomaterials have been introduced into colorimetric sensing systems, which provide significantly improved sensitivity in various biosensing applications. Here we review the recent progress on these plasmonic nanoparticles-based colorimetric nanosensors for ultrasensitive molecular diagnostics. According to their different colorimetric signal generation mechanisms, these plasmonic nanosensors are classified into two categories: 1) inter-particle distance-dependent colorimetric assay based on target–induced forming cross-linking assembly/aggregate of plasmonic nanoparticles; and 2) size/morphology–dependent colorimetric assay by target-controlled growth/etching of the plasmonic nanoparticles. The sensing fundamentals and cutting-edge applications will be provided for each of them, particularly focusing on signal generation and/or amplification mechanisms that realize ultrasensitive molecular detection. Finally, we also discuss the challenge and give our future perspective in this emerging field.

Keywords localized surface plasmon resonance; colorimetric sensor; nanoparticles; biosensor; biomarkers; point–of–care testing; molecular diagnostics; clinical diagnostics

Molecular diagnostics is fundamental in the prevention, identification and therapeutics of various diseases, and therefore the development of powerful diagnostic tools is critically important.[1-4] For example, *in vitro* detection of biomarkers at trace level can help in early diagnosis and therapeutics. Traditional diagnostic techniques including polymerase chain reaction (PCR), enzyme–linked immunosorbent assay (ELISA) and mass spectrometry (MS) have been extensively used in clinical practice, however, they are still limited capability in detecting many biomarkers with low abundance, which are of potentially high clinical relevance.[2,5-8] Apart from the issues in sensitivity and specificity, the established methods are often not allowed for cost–effective, on–site and timely diagnosis, because most of them are expensive, labor–intensive, time consuming and require high skills for operators. To keep up with the increased demand molecular profiling of disease and personalized health care, therefore, further development towards new–generation ultrasensitive diagnostic technologies are eagerly awaited.

Due to the simplicity, reliability and promising in the point–of–care (POC) testing, colorimetric format–based assay point toward their use as one general method for molecular diagnostics.[2,9-14] For example, the colorimetric ELISA is one of the most used diagnostic techniques, which employs enzyme label to trigger colorimetric catalytic reactions for signal output.[10,13] In such assay, the enzymes catalyze the oxidation of chromogenic molecules and then induce the color appearance of the solutions, which is easily naked-eye observed or quantified by a simple UV−visible spectrophotometer. This traditional method, however, has the limitation in the

detection sensitivity for the colorimetric assays, which influenced by several key factors: first, according to the law of Beer-Lambert, the extinction coefficients of the organic chromogens often limit the sensitivity for the traditional colorimetric sensors; second, the traditional colorimetric strategy basically relies on the optical density variation of the colored product, whereas our eyes are not insensitive to the shading of a color, making its difficulty to distinguish targets between samples with naked–eye inspection; third, the enzymes are often utilized as the biological catalysts in enzyme cascade amplification strategy, as thus to keep catalytic activities of enzyme is critical in the process of transportation, storage, and use. Over the past few years, to develop better colorimetric sensors for visual detection of ultralow concentration of analytes, many various concepts have been proposed to tackle these limitations, including using signal amplification strategy and advanced nanomaterials with extraordinary physi-chemical properties, particularly the plasmonic nanomaterials.[2,3,9-12,15-17]

Plasmonic nanomaterials including gold nanopaticles (AuNPs) and silver nanoparticles (AgNPs), armed with unique plasmon resonance properties, are providing new opportunity for colorimetric sensors.[1-3,6,11,18] Since its pioneered work by Mirkin and co-workers in 1997,[19] the plasmonic nanoparticles–based colorimetric assay has drawn dramatically increased interests. In such colorimetric assay, the color generation is caused by the change of optical absorbance properties plasmonic nanoparticles. Importantly, the absorbance (i.e., color) of the nanoparticles is easily modulated by their shape/morphology, size, distribution, metal composition as well as the local environment. Additionally, the plasmonic nanoparticles normally have

ultrahigh extinction coefficients (e.g., 2.7×10^8 M^{-1} cm^{-1} for AuNPs with diameter of 13 nm),[20] thereby a much improved sensitivity can be achieved, enabling the ultrasensitive detection of target molecules.[2,3,6]

To date, although many reviews have extensively detailed the preparation and functionalization of plasmonic nanomaterials as well as their applications in (bio)sensing and imaging,[2,3,6,9,11,18,21,22] none of them has focused on an instructive and complete review of the exciting advancement in the topic of using plasmonic nanomaterials for colorimetric molecular diagnostics. Thus, we here intend to present an authoritative overview of the plasmon–associated colorimetric nanosensors for molecular diagnostics and address on their latest development and progresses in the past five years (typically 2012~2016). In this review, we first briefly introduce the sensing mechanism behind the colorimetric detection system with plasmonic nanoparticles, and then provide a comprehensive coverage of their typical molecular diagnostics applications with different strategies. According to the different signal generation mechanism from plasmonic nanomaterials, the molecular diagnostics strategies will be mainly categorized into inter–particle distance–dependent and size/morphology–dependent colorimetric plasmon nanosensors (**Figure 1**). With each of them having important merits, we will systematically overview their latest progress and current standing in the biosensing field, including their integration with different signal amplification strategies (e.g., enzymatical reaction, polymerization, nucleic acid thermal amplification) and POC analysis systems. Finally, we offer new perspectives on the further development of these colorimetric assays in molecular

diagnostics.

Figure 1

■ PLASMONIC NANOPARTICLES-ASSOCIATED COLORIMETRIC SENSORS

Plasmonics refers to the phenomenon because of the free electrons oscillations on the metal surface under light stimulation.[18] When incident light has the same frequency as that of the surface electron oscillating against the attraction force to their positive nuclei, the resonance can be achieved, which is also described as surface plasmon resonance (SPR, see Figure 2).[23] Typically, two SPR modes have been explored: one is propagating surface plasmon resonance (PSPR) at the flat dielectric–metal interface; the other is localized surface plasmon resonance (LSPR) when those plasmons are highly confined to the surface of the colloidal nanoparticles or other nanostructures (e.g., two-dimensional nanostructured array).[23-26] While the PSPR can propagate surface electromagnetic waves at metal surface, it is the LSPR to be the central of this review.

Figure 2

In plasmonic nanostructures, especially those made from gold and silver, the LSPR yields highly confined and enhanced electromagnetic fields on the boundary of nanoparticle surfaces, together with the appearance of a pronounced absorption peak in the visible and near infrared frequency range.[9] This implies that the nanoparticles' size, shape, surface coating and dielectric environments as well as the nanoparticles–

chemical entities interaction can influence the oscillations, and these events can be transformed to the LSPR spectral change in either absorption/extinction or scattering, and even color variation of the plasmonic nanoparticles solutions.[25] These extraordinary plasmonic phenomena have given rise to a fast–developing field in colorimetric nanosensors, where the introducing of the targets induces the LSPR shift of plasmonic nanoparticles and is accompanied by the color change of the solution either by forming cross–linking assembly/aggregate or transforming size/morphology of plasmonic nanoparticles. According to the different signal generation mechanism, these ultrasensitive assays will be summarized into two categories of inter-nanoparticle distance–dependent colorimetric assay and nanoparticles' morphology/size–dependent colorimetric assay.

1. Inter-particle Distance–Dependent Colorimetric Assay with Plasmonic Nanoparticles. The aggregation of plasmon nanoparticles with appropriate sizes (diameter > 3.5 nm) will induce the surface plasmon coupling between the neighboring particles, along with the LSPR shift and visible color transition of nanoparticles solution.[27] For example, the AuNPs aggregation (or re-dispersion) events correspond the tonality transition of the solution from red to blue (or from blue to red).[19] Therefore, this inter-particle distance–dependent optical property of plasmonic nanomaterials provides a practical basis of the colorimetric assays for the sensing of any targets, such as metal ions, small molecules, macromolecules or living cells.[1-3,6,9,11,21] In this section, we will systematically overview the molecular

interactions driving the aggregates of plasmonic nanoparticles and their applications in molecular detection, which has been rarely focused in the other reviews.

From the technological point of view, the interactions among plasmonic nanoparticles are finely modulated by various covalent/non-covalent forces, including electrostatic interactions, hydrophobic forces, hydrogen bonding and specific biological bonding.[28-32] During the driving plasmonic nanoparticles interaction, these forces are largely interrelated and easily affected by many external factors, such as temperature, pH and buffer solution. Therefore, it will be challenging to completely unfold the basic principles for each inter-nanoparticles interactions.[28] In this section, we will only highlight the methodology of using each of driving forces to control the inter-distance of the nanoparticles, and illustrate the important role of surface coating/modification of plasmonic nanoparticles in the colorimetric sensing applications.

1.1 Electrostatic interactions. An Electrostatic interaction or bond is frequently used for the buildup of assembled plasmonic nanostructure. When plasmonic nanoparticles surfaces (especially AuNPs and AgNPs) are electrically charged, the electrostatic interaction can facilitate the nanoparticles assembly. Under the purely electrostatic interactions, the external stimuli including various surrounding environments (e.g., pH, ionic strength, electrical field, light, temperature, mechanical stress) or the introducing of specific biomolecular species (e.g., proteins, DNA) may influence the nanoparticles surface and even control aggregation or re-dispersion of nanoparticles, thus resulting in a LSPR change. Based on these stimuli-responsive capabilities,

numerous studies have been reported on electrostatic interactions-involved plasmon-based colorimetric assay.[1,6,9,11] A problem, however, is that the detection sensitivity for direct quantification is usually insufficient due to the inherent weak force of electrostatic interactions. Indeed, except for the using multivalent electrostatic interactions, many other methodologies have been proposed to amplify the interaction forces during nanoparticles aggregation events and improve the sensitivity, particularly the combination of enzymatical catalysis, polymerization and other highly efficient physi-chemical reactions (**Table 1**).[33-47]

Table 1

Thiol compounds including L-cysteine and homocysteine have high binding affinity to AuNPs through the Au−S bonding, Because of the existence of deprotonated carboxyl group and protonated amine group of cysteine, the AuNPs are apt to aggregate via the electrostatic interaction among cysteine-modified AuNPs. In contrast, disulfide cystine can form monolayer on gold surface, resulting in increased steric hindrance to prevent aggregation of AuNPs. Thus, through controlling the amount of cysteines or their oxidation process, the cysteine-stimulated aggregation of AuNPs could be used as an auxiliary reporting system for AuNPs-based colorimetric nanosensor systems.[35,48-50] For examples, with the catalytic capability of Cu^{2+} in the oxidation of thiols to disulfide, Lu *et al.* developed a plasmon-based colorimetric sensor for the sensitive detection of Cu^{2+} and proteins using citrate-capped AuNPs.[48] Alternatively, in the presence of H_2O_2, iodide can also catalyze the oxidation of cysteines to form disulfides.[50] As H_2O_2 can be produced by glucose oxidase

(GOx)-biocatalyzed oxidation of glucose yields or depleted by HRP oxidation reaction, the H_2O_2-related biocatalytic reaction could be monitored by the similar cysteine-modified colorimetric sensing system.[50] For example, Jiang group employed HRP-catalyzed oxidation of iodide and iodide-catalyzed oxidation of cysteine to modulate the dispersion/aggregation of AuNPs so as to achieve ultrasensitive colorimetric detection (**Figure 3**).[35] In this strategy, the HRP-triggered cascade reaction can achieve naked-eye readout with enhanced sensitivity. Otherwise, Abbas and coworkers developed an enzyme-free plasmonic colorimetric sensor with signal amplification via cysteine-loaded liposomes (**Figure 4**).[46] The introducing of a single pathogen in the sample would trigger the breakdown of cysteine-loaded nanoliposomes and subsequent aggregation of AuNPs. Moreover, the lowest concentration of target antibody detected with naked eye was down to 6.7 attomolar (aM), which was much lower than conventional ELISA.

Figure 3 and Figure 4

To enhance detection sensitivity, the acetylcholinesterase (AChE)-based hydrolysis has also been integrated into plasmon-based colorimetric assay.[36,38,51,52] AChE is a serine protease with high efficiency in hydrolyzing its substrate acetylthiocholine (ATC) to a sulfhydryl compound, thiocholine. The produced thiol group on thiocholine can covalently attach onto the surface of plasmonic nanoparticles (especially AuNPs), resulting in the positive charges on the nanoparticles. The alteration of the surface charge distributions facilitates much stronger electrostatic interaction between the nanoparticles, and thus changes the agglomeration state of

plasmonic nanoparticles. Based on this AChE-amplified sensing system, Liu *et al.* developed a sensitive colorimetric assay for specifically monitoring the activity of AChE and their inhibitor screening (**Figure 5**).[51] In this work, AChE catalyzed the conversion of ATC to thiocholine, which would bind to the surface of AuNPs and meanwhile facilitated the ligands replacement, resulting in nanoparticles aggregate and Rhodamine B released from nanoparticles surface. Thus, this system provided dual-readout signals (both in fluorescence recovery and color change). Using this AuNP-based dual readout assay system, the level of AChE in complex fluid was successfully monitored with a high detection sensitivity (0.1 mU mL^{-1})[51] Chen and co-workers reported the combination of AChE-catalyzed hydrolysis reaction with AuNPs-based colorimetric sensing platform for ultrasensitive colorimetric sensing of pathogen even in clinical samples (**Figure 6**).[36]. Later on, Lu and Xia depicted the strategy using AChE reaction to modulate the cysteine-based aggregation of gold nanorods (AuNRs) and utilized in the colorimetric assays for organophosphate pesticides (OPs) and cholinesterase (ChE) in human blood.[52] Similarly, Nie *et al.* employed this sensing method for detection of *Treponema pallidum* (*T. pallidum*) antibodies, with a limit of detection down to 0.98 pg mL^{-1}.[38] The above studies have well demonstrated that the inclusion of AChE-based enzymatical reaction could effectively enhance the sensitivity of plasmon-based colorimetric sensing.

Figure 5 and Figure 6

Besides, polymers are often utilized to improve the stability and dispersion of

nanomaterials, but also capable of bridging nanoparticles together resulting in entanglement and aggregation. This nanoparticles/polymer assembly process can be driven by electrostatic interactions, hydrogen bonding, or more specific molecular interactions. Such assemblies have useful applications in drug delivery, biosensing, and catalysis. Recently, Stevens and co-workers described a new assay format that uniquely takes advantage of polymerization based signal amplification, by using GOx to trigger free-radical polymerization of a cationic monomer to control the AuNPs aggregation. Such a design takes advantage of polymerization-based signal amplification, and could be used to detect low concentrations of enzymes (e.g., HRP and catalase) and metal ions (e.g., iron and copper) with the naked eye. Given that polymerization based signal amplification is currently limited by appropriate readout methods, it is anticipated that this new platform will provide tools for biosensing.

1.2 Covalent Bonding. Covalent bonding can enable to fabricate stable well-defined assemblies from plasmonic nanoparticles, such as multilayer structure. In addition, this inter-molecular interaction allows to incorporate several other functional groups on to nanoparticles surface by reacting through excess reactive groups, resulting in the tailored multifunctional assemblies. Although covalent bonding is lack of the flexibility in the self-assembly process compared to other forces, it may provide higher binding force among the building block, resulting in improved assembly efficiency and thereby enhancement of the sensitivity and shorter detection time in colorimetric assay, as a particular example of the use of click chemistry.[13,34]

The versatile surface chemistry of covalent bonding can facilitate the use of functionalized plasmonic nanoparticles for fabricating colorimetric sensors.[1,41] For example, Stevens *et al*. utilize peptide-functionalized AuNPs as colorimetric sensing platform for monitoring the activity of blood coagulation Factor XIII.[41] The Factor XIII catalyzed the formation of covalent crosslinking among the peptide chains-functionalized AuNPs through ε-(γ-glutamyl)-lysine bonds, corresponding to the nanoparticles aggregation and a color change in nanoparticles solution. The colorimetric assay allowed highly sensitive analysis of Factor XII activity down to 0.01 U mL^{-1}.

Alternatively, the click chemistry reactions-based covalent bonding, especially Cu(I)-catalyzed 1, 3-dipolar cycloaddition of azides and alkynes (CuAAC), has been widely used in plasmon-based colorimetric nanosensors.[13,34,53] In this strategy, AuNPs were typically modified with azide and alkyne groups by the ligand exchange reaction, and thus the existence of Cu (I) would trigger the CuAAC reaction and then crosslink the azide-AuNPs and alkyne-AuNPs to cause their aggregation. This aggregation of nanoparticles leads to the color change of AuNPs from red to blue, and the status of aggregation can be correlated to the concentration of Cu (I). This methodology has been employed for the detection Cu(I), Cu(II) (by reducing Cu(II) into Cu(I)) and many other related targets, such as reducing agents to Cu (II) (e.g. ascorbic acid and NO)[54,55] and biological molecules.[34,53] For example, Jiang *et al.* utilized the CuAAC-mediated AuNPs aggregate for colorimetric immunoassays of proteins by indirect detection of Cu(II). They proposed to use copper monoxide (CuO)

nanoparticles to conjugate with secondary antibody instead of the enzyme label in the conventional immunosensensors. After the immunoreaction procedures, the labeled CuO nanoparticles would be dissolved by acid to release Cu (II) and further reduced to Cu(I) which then initiated CuAAC reaction (**Figure 7**). This colorimetric immunoassay can therefore be used for many applications, including POC-format assays. Actually, the formation of Cu(I) to trigger CuAAC can be realized by the other classically enzymes, such as akaline phosphatase (ALP).[34] Under ALP-catalyzed dephosphorylation process, ascorbic acid-phosphate can be transformed into ascorbic acid, which acts as a reducing agent to react with Cu(II) to generate Cu(I). Based on the ALP-mediated transforming Cu(II) to Cu(I), Jiang and coworkers developed a CuAAC-based immunosensors for naked-eye detection of 80 ng mL^{-1} rabbit antihuman IgG. This CuAAC-amplified naked-eye detection presented an enhanced sensitivity than conventional immunoassay.

Figure 7

1.3 Hydrophobic Interaction. Hydrophobic interactions, as the nonspecific interactions, are important in biological systems (e.g. lipid bilayers). By tuning the solvent composition and the hydrophobic property on nanoparticles surface, hydrophobic interactions are often used for the buildup of nano-assembly or multilayer films. For example, they have been proposed to be the the main driving force to initiate the solvent-induced assembly of hydrophobic AuNPs into three-dimensional (3D) clusters.[56-59] In combination with a unique set of optical properties of plasmonic nanomaterials such as LSPR, the hydrophobic interactions

can be potentially used in both biosensing and nanomedicine. Specifically, the fabrication of amphiphilic plasmonic nanostructures with polymer brushes could be extended for molecular diagnostics, biomedicine and treatment.[56-58] For instance, through the amphiphilicity-driven self-assembly of hybrid nanoparticles, plasmonic nanoparticles can be embedded in the well-defined vesicles with collapsed hydrophobic polymers. Becuase of the strong plasmonic coupling effect, greatly, the plasmonic vesicles have enhanced optical properties (e.g. scattering, SERS, photothermal conversion) and extend to application in single particle plasmonic imaging, photothermal therapy and photoacoustic imaging.[58] By tuning the strength of hydrophobic interaction between biopolymer DNA and AuNPs, Lin *et al.* recently proposed a colorimetric detection of DNA methylation[59] In this method, hydrophobic interactions would influence the DNA solvation and thereafter the short-range gold–DNA interactions, because of the requirement of dehydration of DNA-bases (or DNA-backbone) during DNA–gold adsorption event. The resulted sensing assay could naked-eye discriminate the methylation level of nasopharyngeal carcinoma cells, and even distinguished the heterogeneity of DNA methylation in twelve cancer cell lines, predicting its possibility in epigenetic studies.

1.4 Biologically Specific Interactions. The specific interactions between biological molecules include multiple intermolecular forces, such as hydrogen bonding, hydrophobic and electrostatic interactions, and importantly they provide specific recognition to the targeting molecules. In the past several decades, the biologically specific interactions have enlarged the nanomaterial structures and functions. Through

the biological forces, various nanomaterials have been self- assembled to functional films, and extended in the (bio)sensing, medicine and other applications. Based on the biologically inter-molecular interaction, including avidin−biotin, antibody−antigen, carbohydrate−protein interactions and DNA hybridization, kinds of colorimetric plasmon nanosensors have emerged over the years. In the light of their most established and emerging applications, we here introduce and discuss the DNA hybridization and carbohydrate−protein interactions−involved plasmonc colorimetric assays.

Various nucleic acids-based recognition units coupled with plasmonic nanoparticles have been well established in the colorimetric sensors.[6,33,37,39,44,60-64] Typically, these colorimetric sensors involved the AuNPs functionalized with either a probe DNA or a functional DNA (e.g., aptamer and DNAzymes) for capturing the target analytes. When complementary DNA or other targets were added into the AuNPs probes solution, the DNA hybridization would result in the nanoparticles aggregation with a color change and then enable the quantitative colorimetric detection of targets. The AuNPs-based colorimetric assay relies on the formation large AuNP aggregates by DNA hybridization, therefore the sensitivity and dynamic detection range are usually limited at the nM level. This sensitivity is insufficient for DNA biomarkers in most clinical samples where their concentrations generally range from aM to pM. In the past several years, many effective amplification strategies were integrated into the naked-eye nanosensors with an enhanced sensitivity. Chan *et al.* combined the DNAzyme catalyzed amplification strategy for diagnosis of infectious

diseases.[63] With this enzyme-catalyzed signal amplification, a limit of detection for target DNA down to 50 pM could be achieved, much lower than those using direct AuNPs assays. Recently, Valentini *et al.* utilized the versatility of PCR to amplify the DNA-based colorimetric detection for HIV template DNA down to 0.01 zeptomoles (zM) (**Figure 8**).[37] Alternatively, isothermal (PCR-free) amplification was also used for the naked-eye detection of cancer-related point mutations, with the detection limit in the low pM range.[33] In such amplification, the helicase-dependent isothermal reaction was permitted high amplification efficiency and meanwhile avoids the complicated thermal cycles in the traditional PCR. This colorimetric nanosensor could provide more sensitive detection for single mismatch discrimination up to 4 orders of magnitude compared to the AuNP-based direct colorimetric assays.

Figure 8

Through carbohydrate−protein interactions, plasmonic nanoparticles can be controlled assembled and developed into colorimetric sensing platforms for monitoring various carbohydrates and proteins.[1] Geddes *et al.* have explored the self-assembly of dextran and concanavalin A (Con A)-modified AuNPs for competitive colorimetric sensing of glucose.[65] Besides carbohydrate, carbohydrate−binding proteins could also be detected based on the lectin−carbohydrate interactions−involved colorimetric plasmon nanosensor. For example, Kataoka *et al.* reported the using controlled assembly of β-D-lactopyranoside (Lac)-modified AuNPs for the naked-eye detection of *Ricinus communis* agglutinin (RCA_{120}, a ricin surrogate).[66] In this method, the protein RCA_{120}

concentration could be related to the dispersion/aggregation status of nanoparticles, thus allowing the quantitativel detection of lectin. Significantly, when these AuNPs were functionalized with the galactose derivative with thiolated group, a detection limit of 9 nM for RCA_{120}could be achieved. In an alternatively study, Con A could be identified through controlling the aggregation of mannose- and Con A- modified AuNPs.[67] Similarly, other carbohydrate-binding protein can be sensed by the manno- and gluco-oligosaccharide-coated AuNPs using the lectin Con A.[68] Russell *et al*. employed Lactose-stabilized AuNPs to determin the calcium ion-mediated carbohydrate-carbohydrate interactions.[69] Uzawa *et al*. utilized the functional AuNPs with different synthetic sugar probes for discriminating ricin toxin at nM level.[70] Likewise, sialic acid modified-AuNPs could be utilized for the colorimetric detection of JC virus VLPs via sialic acid recognition.[71]

1.5 Host−Guest Interactions and Others. The host–guest interaction exists in the molecular system, where a host molecule can recognize and bind a certain guest molecule. This interaction plays an important role in the supramolecular systems or materials because of its high efficiency, good selectivity, and stimuli responsiveness.[29] In plasmon-based colorimetric assay, the controlled assembly of plasmonic nanoparticles can be achieved using the host−guest systems. For example, since Cucurbit[8]uril (CB[8] (CB[8]) can accommodate with two N-terminal aromatic residues of peptides, the introducing of CB[8] will trigger the cross-linking aggregation of the peptide-modified AuNPs. Based on this effect, a low concentration of 0.2 nM for tumor biomarker Flt-1 could be achieved, comparable with traditional

methods.[40] Wen *et al.* also demonstrated beta-cyclodextrin modified-AuNPs could be directly employed as optical probes for colorimetric detection of dopamine.[72]

Indeed, other non-covalent interactions including metal coordination and aromatic stacking, van der Waals forces can be employed as driving forces in plasmon-based colorimetric nanosensors. For example, the interaction between chelating ligands and metal ions has been used for the colorimetric detection of metal ions, in which chelating agents were generally functionalized on the nanoparticles. The introducing specific ion could induce the nanoparticles aggregation because of the chelating ligand-mediated forming cross-linked complexes. Chen *et al.* used 15-crown-5 moieties-modified AuNPs for the naked-eye detection of potassium ions (K^+) because of the interaction between 15-crown-5 moiety and K^+.[73] Hupp and coworker reported utilizing 11-mercaptoundecanoic acid (MUA)-modified AuNPs for the naked-eye detection of heavy metal ions.[74] In such colorimetric sensor, the surface-attached carboxylates act as metal ion receptors and the related heavy-metal ion chelation process induce the color change (red to blue). Similarly, Li^+ and Ca^{2+} have been detected by phenanthroline-modified AuNPs [75] and lactose-functionalized AuNPs, respectively.[69]

2. Plasmonic Nanoparticles' Morphology/Size–Dependent Colorimetric Assays. Besides the inter-nanoparticle distance–dependent mechanism (i.e., target–triggered inter-particles cross–linking or aggregation) for colorimetric plasmon nanosensors, the precise tuning of the morphology/shape and size of plasmonic nanoparticles have

also been applied for the colorimetric sensing in the target–mediated molecular events. Since the nanoparticles growth can be tuned by many synthetic parameters, such as precursor, reducing agents, capping agents and others, there have been numerous reports on the controlling growth with some key parameters, i.e., very small change will result a totally different resulted nanoparticles, yielding differentiable features in the optical properties, particularly LSPR. Therefore, through tuning the kinetics of growth/etching of plasmonic nanoparticles, a variation of LSPR and solution color can be easily identified, and thereby the morphology/size–dependent properties can be controlled by some target–induced recognition events. In the light of the evolution approach in the size and morphology of nanoparticles, the related colorimetric nanosensors will be categorized and overview i) target-induced plasmonic nanoparticles growth– and ii) plasmonic nanoparticles etching– dependent colorimetric assays.

2.1 Target–Induced Plasmonic Nanoparticles Growth for Colorimetric Assays. Specifically, the biomolecular–related reducing agents have been chosen as the key parameter for the controlling the nanoparticles growth. With this, hydrogen peroxide (H_2O_2) and other reducing agents can be quantified by the plasmonic nanoparticles growth–based sensing mechanism.[76-79] For example, H_2O_2 can reduce $AuCl_4^-$ (or Ag^+) to Au(0) [or Ag(0)], thus enlarging the seeding AuNPs (or AgNPs) and leading to an obvious LSPR change. However, the growth of plasmonic AuNPs is largely determined by the concentration of H_2O_2. Thus, based on the mechanism, H_2O_2–controlled nanoparticle growth can be combined and developed into novel plasmonic

colorimetric nanosensor. Keunen *et al.*[77] reported using H_2O_2 to control the synthesis of gold nanoparticles with highly symmetric stellated structure (AuStNPs) and sensing for iodide. They found the stellation of AuStNPs could be controlled by multiple synthetic parameters including the used seed particles, reaction conditions, etching agent of iodide. under the regulation of the size and degree of stellating of AuStNPs, the LSPR was varied from *ca*. 850 nm to *ca*. 530 nm. Based on this, they demonstrated its sensing for Iodide sensing with a limit of detection as low as 3.2 pM. Liu and coworkers recently reported a wash–free homogeneous plasmonic colorimetric immunoassay combined with the controlled growth of AuNPs in aqueous solutions.[79] In this strategy, the inter-particle spacing in the protein–AuNP oligomers was modulated by the controlled growth on the the AuNPs aggregate. Upon the gold growth, the particle size was enlarged and the inter-particle distance decreased, thereby inducing a visible optical transition. With this approach, the *in vitro* detection of cancer biomarkers (e.g. CEA) in serum samples from patients' needs only 30 s by the naked eye. Because of its rapid and convenient sensing advantages, this resulted colorimetric immunoassay may allow the timely diagnosis.

As the aforementioned, this epitaxial growth on nanoparticles can be effectively linked with the catalytic enzymes, such as GOx (generating H_2O_2) and catalase (consuming H_2O_2).[80-85] This relationship could be the basis for the fabrication of the plasmon-based colorimetric nanosensors. The solution parameters for nanoparticles growth (e.g. reducing agent, pH, *etc*.) can be associated with the kinetic reaction of a specific enzyme. Thus, the enzyme–mediated plasmonic nanoparticles growth can be

easily integrated with colorimetric plasmon sensing systems for various analytes, especially the conventional ELISA format.[85] Importantly, the signal generation mechanism includes an enzymatical and chemical cascade reaction during growth, leading to a significant increase in sensitivity. Potentially, all enzymes including natural enzymes and artificial enzymes, which are able to catalyze the decomposition of enzymatic substrates to reducing agents, can promote generation of metal nanoparticles. In such colorimetric assay, various enzymes including oxidase, catalase, alkaline phosphatase, dehydrogenase and acetylesterase have been proposed to control the growth of plasmonic nanoparticles and explored for various molecular detection (**Table 2)**.*[27,76,79,83-97]*

Table 2

GOx is a robust and available enzyme in catalytic oxidation of β−D–glucose with O_2 to produce D–gluconolactone and H_2O_2. Consequently, by the epitaxial growth of nanoparticles can be controlled by the amount of GOx. This relationship could be the basis for the GOx-mediated plasmon-based colorimetric sensing. Stevens *et al.* demonstrated GOx could control the epitaxial growth on AuNPs, and extend to the development of a new plasmonic nanosensor with inverse sensitivity, in which a lower concentration of analyte induces a larger LSPR shift.[85] This inverse plasmonic assay allowed for the detection of PSA at ultralow concentration even in whole serum, with a limit of detection as low as 10^{-18} g mL^{-1}. This strategy provides a great opportunity for developing ultrasensitive plasmonic to detect DNA, RNA or other analytes. Yan and coworker further combined small sized AuNPs anchored on

magnetic beads (MBs), acting as dual functionalities of signal production and magnetic separation, for naked–eye detection of thrombin.[83] Since the extinction coefficients of AuNPs are highly dependent on the size of particle, the small sized AuNPs (diameter <5 nm) solution under low concentration (normally <10 nM) was colorless, whereas the solution with the same concentration of the larger sized nanoparitlce usually appeared to be red. Based on this fact, Xiong *et al.* Utilized 5 nm AuNPs as seed for GOx–catalyzed growth and developed a simple colorimetric assay for glucose (**Figure 9**).[84] Furthermore, Liu and co–workers,[82] recently utilized the GOx–controlled growth system with 5 nm AuNPs for quantitative detection of attomolar PSA. By virtue of this strategy, the naked–eye low detection limit for PSA was down to 93 aM (60 fg mL^{-1}) and a wide linear dynamic range (4 orders of magnitude) was obtained in patient serum, indicating their capability for clinical detection.

Figure 9

Otherwise, catalase can efficiently decompose H_2O_2, thereby allowing catalase as the enzyme label in nanoparticle growth-based colorimetric assays.[27,86,90,94,95,98,99] Stevens and coworkers combined this catalase–controlled nanoparticles growth with traditional sandwich immunoassay and developed to the new plasmonic ELISA, where the catalase was conjugated onto the second antibody[95,98] When the analytes were absent, abundant H_2O_2 induced the quick reduction of Au^{3+} and thereby resulting in dispersed spherical AuNPs with the appearance of red color. By contrast, when the analytes was present, H_2O_2 was consumed by the catalase labeled on the

secondary antibody and retarded the AuNPs enlargement, leading to the aggregation of AuNPs and correspondingly a blue solution (**Figure 10**). They utilized the sandwich immunoassays for test of HIV–1 capsid antigen p24 and prostate specific antigen (PSA). In both cases, a detection limit of 10^{-18} g mL^{-1} was achieved in whole serum. Later on, this sensing strategy was extended to the naked–eye detection of other targets, such as methyltestosterone (MT, a growth promoter during the cattle production cycle) [27], HIV–1 protein gp120 [94] and bacteria *Salmonella typhimurium* (*S. typhimurium*).[90] Through catalase carrier to load more enzyme labels, a higher sensitivity could be achieved. Chen and coworkers immobilized catalase on SiO_2–based nano-spherical brushes for enhancing the detection sensitivity for *Listeria monocytogenes* (*L. Monocytogenes*) with 5 orders enhancement compare to the conventional HRP–based immunosensor.[86] Similarly, Zhao *et al.* utilized catalase–functionalized SiO_2 nanoparticles for the colorimetric sensing of microRNA, which could provide an high amplified colorimetric signal and improve the assay sensitivity down to aM level.[99]

Figure 10

Besides H_2O_2-related enzymes, the hydrolytic enzymes including alkaline phosphatase (ALP) have been extensively used in plasmon-based colorimetric assay.[87,89,91,93,100] In this strategy, ALP can catalyze the dephosphorylating of some specific phosphate–contained substrates, such as ascorbic acid–phosphate and p–aminophenol–phosphate, the generated molecules (eg., ascorbic acid, p–aminophenol) enable the reduction of metal ions (e.g., Au^{3+} and Ag^{+}) and enlarge the metal seeds

(e.g., AuNPs and AgNPs). If using a sandwich–format immunoreaction, the target can be quantified by the color change. Zhou *et al.*[89] combined ALP–induced silver growth on the AuNP and immuno–magnetic separation for the visual sensing of ALP and avian influenza virus (**Figure 11)**. In another example from Yang et al.,[93] they utilized AuNRs as seeds in the ALP–mediated plasmonic ELISA (**Figure 12**). AuNRs, as anisotropic nanocrystal with well–defined and controllable shapes, are highly sensitive to the variations in local refractive index, thereby leading to the LSPR change and providing the possibility of use in the sensitive colorimetric nanosenosr. In this colorimetric sensing system, the enzyme label of ALP could control the growth of ultrathin silver shells on the AuNRs. In the presence of antigen, ALP was first carried by a silica particle through a sandwiched structure, and then catalytically produced 4–aminophenol, which consequently depositing the silver layer on AuNRs, thus resulting in the LSPR shift of AuNRs along with a color change. For the detection of PSA, 10 fg mL^{-1} target can be effectively detected, which was 10^4–fold enhancement over conventional ELISA, exhibiting a highly efficient signal amplification .

Figure 11 and Figure 12

Alternatively, other enzymes including dehydroganase and acetylesterase, have also been introduced into the plasmonic nanoparticles' growth-based colorimetric assays. [88, 102,104] Dehydroganase, belonging to oxidoreductases, oxidizes a substrate by a reduction reaction to transfer one or more hydrogens to an electron acceptor, usually being NAD^+/$NADP^+$ or a Flavin coenzyme. Since the reduced form of the enzymatic

cofactor NADH is able to reduce metal ions (Au^{3+} or Ag^{+}) to deposite onto seeding AuNPs, the NAD^{+}–dependent dehydrogenases, for example, alcohol dehydrogenase (ADH) allows for the fabrication the nanoparticles growth–based colorimetric sensing system in solution.[88,92,101-103] Long and coworkers reported a strategy–based plasmonic ELISA using ADH-mediated gold growth on AuNPs to generate the colorimetric signal generation for the naked-eye detection of disease biomarkers (**Figure 13**).[88] Otherwise, esterases can hydrolyzed esters to an alcohol and an acid in a chemical reaction, which has been well used in the biosensing application, specifically like AChE and lipase [104]

Figure 13

Besides the above natural enzyme, artificial enzymes have also been explored to control the nanoparticles growth and apply for the plasmon-based colorimetric sensing system. The artificial enzymes are kinds of synthetic organic molecule or nanomaterials with enzyme–like characteristics, including nanozymes and artificial DNAzymes. Nanozymes are kind of nanomaterials with enzyme–like characteristics, including nanoceria (i.e., CeO_2 nanoparticles), ferromagnetic nanoparticles, iron oxide.[105] In term of biological catalytic effects, a number of examples have shown the inorganic nanoparticles could mimic the action of enzymes. For example, it is found that GNPs can mimic the catalytic activity of GOx, which catalyzing the glucose oxidized to glucolactone and simultaneously produced H_2O_2. By taking advantage of the GOx–like oxidization effects, Li *et al.* reported a AuNPs–based catalyzed system for monitoring blood glucose and detection of DNA hybridization.[76] More recently,

Zhao reported the utilizing the gold nanoclusters (AuNCs) as the mimetic enzyme for ultrasensitive plasmonic ELISA, which enabled the visual detection of ultratrace targets through naked–eye readout (**Figure 14**).[76] They expanded this strategy to detect other analytes, indicating the promising for practical applications.

Figure 14

DNAzymes, also called deoxyribozymes or DNA enzymes, are catalytically active DNA molecules. It can be utilized as label to signal out and amplify the sensing event in plasmon-based colorimetric assay. Wang and coworkers used the HRP–mimicking DNAzymes to modulate the AuNPs growth and apply in the plasmonic detection of thrombin.[92] An ultralow detection limit of 10 aM thrombin was achieved, with greatly improvement in the sensitivity compared to the traditional colorimetric methods using AuNPs. Compared to the natural enzyme label, artificial enzymes with high catalytic capabilitys can be easily synthesized and modified with low cost, as well as more stable against stringent conditions.

2.2 Target-Induced Plasmonic Nanoparticles Etching for Colorimetric Assays. Controllable chemical etching, as one of most vital strategies for controlling the nanostructure, has been used in electronic, catalysis and optic sensing applications, including in the plasmon-based colorimetric sensing systems. Usually, it involves the oxidation of plasmonic nanoparticles in the presence of the etchant, leading to the composition/morphology change of the nanoparticles, which can be naked-eye detected. For example, the etching of silver triangular nanoplates (also called silver nanoprisms, silver TNPs) can reshape in the presence of H_2O_2 or halides to yield

silver nanodisks. The change in shape from the sharp edges of the triangles to the rounded corners of spherical nanoparticles changes the color of the solution from blue/purple to red or yellow colored depending on the concentration of the analytes. According to the plasmonic nanoparticle-based etching mechanism with specific oxidation agents, we here summarize the recent progress of plasmonic nanoparticles etching–based colorimetric assays, which are categorized to the H_2O_2, heavy metal, and anion mediated nanoparticles etching–dependent colorimetric assays.

2.2.1 H_2O_2–Mediated Etching. Besides using as reducing agent for nanosynthesis, H_2O_2 is also a powerful oxidizing agent for the plasmonic nanoparticles under specific conditions. As we refer to above, H_2O_2 can be produced by the enzymatic oxidation of glucose by GOx or consumed by catalase, the H_2O_2–mediated nanoparticles etching can be developed to plasmon-based colorimetric nanosensors with incorporation of enzyme. Jin and co–workers combined the GOx–responsive hybrid Ag/Au bimetallic nanoshells (NSs) system into plasmon nanosensor for glucose detection.[106] Upon the surface–confined enzymatic oxidation of glucose by GOx, Ag would be selectively dissoluted from the Ag/Au NSs by H_2O_2, resulting in a morphological evolution and the LSPR band of NSs red–shifted gradually. Later on, Xu and coworkers used this similar strategy for *in situ* detection of GOx enzymatic activity.[107] Indeed, the strategy should extend into analytical platform including other H_2O_2–generated reactions, such as the the substrate–enzyames system of choline–choline oxidase, lactic acid–lactate oxidas and glutamate–glutamate oxidase.

Because of their strong shape dependent optical properties, silver–based

anisotropic nanomaterials have been chose as plasmonic probes. Especially, the silver TNPs with 3D sharp tip or corner-like structure will significantly contribute to the surface plasmonic properties and improve the naked–eye sensitivity in the H_2O_2–mediated etching event. Xia *et al.*[108] developed a sensitive colorimetric sensing system with silver TNPs and GOx for the detection of glucose in serum. Liang *et al.*[109] integrated the H_2O_2–controlled etching system into sandwich immuno–assay ELISA format with GOx label for naked-eye sensing of cancer-related biomarkers in serum (**Figure 15**). In the presence of targets, the conjugated GOx on the detection antibodies induced the H_2O_2 etching of silver TNPs and simultaneously a colorimetric blue–to–purple change. The naked–eye detection limit for PSA was down to 4.1 fg mL^{-1}, which was more sensitive than that of the conventional HRP–based immunosensors (1.25 ng mL^{-1}).

Figure 15

With help of the other signal amplification strategies, the sensitivity of H_2O_2 etching-based colorimetric sensors can be further enhanced. Yang *et al.* combined GOx–mediated etching of **s**ilver TNPs with nuclease–free signal amplification and further improved the sensitivity for the naked–eye DNA detection.[110] Recently, Tang *et al.* proposed a plasmonic sensing strategy with bacteria–responsive DNAzyme for detection of target bacteria.[111] Using *Escherichia coli* (*E. coli*) as a model analyte, they demonstrated that the sensing system could provide low concentration (down to 50 bacteria per mL) quantification of *E. coli* even in the complex fluids (e.g., milk, serum, juice) with naked eyes.

2.2.2 Heavy Metals–Mediated Etching. Because of their high oxidation potentials, most heavy metals generally can be used as effective etchants. Under the optimized conditions like temperature, pH, the presence of other reagents, plasmonic nanoparticles can be effectively etched by the specific metal or metal ions, resulting in the spectral shift of nanoparticles solution. On the basis of this mechanism, the heavy metal–mediated etching process can be integrated to plasmon-based colorimetric sensing systems, and developed for the specific and sensitive determination of various metals.[112,113] For example, with the Hg^{2+}–mediated morphology change of 1–dodecanethiol–coated silver TNPs, Chen *et al.* developed a simple colorimetric approach for Hg^{2+} sensing.[114 115] Later on, Zhu and coworkers. reported a colorimetric sensisng platform for Pb^{2+} detection in complex real samples. They found the thiosulfate ($S_2O_3^{2-}$) can adsorb onto positively CTAB–capped AuNR surfaces by the electrostatic interactions [116] and experience the redox reaction to form ($Au(S_2O_3)_2^{3-}$) on the AuNR surface.[117] Because of the formation of Pb–Au alloy ($AuPb_2$ and $AuPb_3$), the addition of Pb^{2+} can significantly increase the etching rate of the gold, which is dependent on the concentration of Pb^{2+} ion. This sensor was further extended into the detection of Pb^{2+} in complex fluids (lake, seawater, urine, and soil samples). Wen *et al.* [118] found the presence of Cu^{2+} even with low concentrations helped dissolution of the surface Au–O complex, thus resulting in the reshaping of GNRs. Based on this observation, Zhang *et al.*[119] and Chen *et al.*[120] developed the sensitive plasmonic nanosensors for naked-eye detection of Cu^{2+}. Liu *et al.* found only $S_2O_3^{2-}$ could be used as a catalyst for Cu^{2+}–mediated etching of AuNRs, and thereby obtained a

detection limit for Cu^{2+} of 220 nM. This sensor has been validated in the detection of Cu^{2+} in human serum and tap water.[121]

2.2.3 Anion–Mediated Etching. The chemical etching of plasmonic nanoparticles can also be triggered by the specific anions including cyanide (CN^-) and halide (e.g., Cl^-, Br^-, I^-), thereby resulted in the colorimetric assays based on anion–mediated etching of plasmonic nanoparticles. CN^- is susceptible to dissolve gold and silver via the formation of the soluble cyano–complex, such as $[Au(CN)_2]^-$ and $[Ag(CN)_2]^-$.[122-124] In the presence of CN^-, AuNRs can be progressively chemical etched at their tips, resulting in the change of AuNRs aspect ratio and subsequently the blue-shift LSPR absorption. *Lee et al.* recently reported cyanide-based colorimetric sensor based on the selectively etching on AuNPs, allowing for the sensitive detection of cyanide with the naked eye (**Figure 16**).[123]

Figure 16

Alternatively, halide ions plays a vital role in the morphology–controlled syntheses and modulating the optical properties of plasmonic nanoparticles. It is known that the adding of iodide ions can significantly influence the morphology of anisotropic nanostructures, such as Au NRs and Au TNPs, because iodide ions can selectively and strongly bind with the Au (111) facet and facilitate the anisotropic growth of nanoparticles. Furthermore, the iodide ions were found to accelerate the selective etching along longitudinal direction of CTAB–stabilized AuNRs, leading to the blue–shifted LSPR absorption peaks and the color change of solution.[125-129] Based on halide–mediated etching of plasmonic nanoparticles, the colorimetric nanosensors

have been proposed for the detection of halide ions and other targets. For example, Liu *et al.* reported a AuNRs–etching colorimetric nanosensor for the naked-eye detection of I^-, with the limit of detection of 0.88 nM.[130] Zhang and coworkers combined the iodine–induced etching of AuNRs for on–site detection of dissolved oxygen (DO).[125] In the assay, the quantitatively detection of target DO could be converted to the detection iodine, which leading to the selective etching of CTAB-capped AuNRs along the longitudinal direction. Under given conditions, they achieved the naked–eye detection of DO in different aqueous samples. Later on, Zhang et *al.* utilized the catalytically formed to mediate the etching of AuNRs and applied for the ultrasensitve visual detection of molybdate.[127]

Besides, the interaction of AgNPs and halide ions has studied and used in the nanoparticles etching–based colorimetric nanosensors, especially with the silver TNPs as the plasmonic indicator.[128] In the presence of I^-, the edges and corners of the silver TNPs are actively and easily coordinate with I^-, resulting in the shape change from nanoprism to nanodisk, along with a distinct color change of solution from blue to red. Huang and coworkers studied the kinetic etching of silver TNPs by halide.[131] With this etching ability of I^-, Jiang and coworker developed a simple sensing approach in the detection of inorganic anions based on the LSPR shifts of silver TNPs.[132] Similarly, Yang *et al.* used the iodide–controlled etching of citrate–stabilized Ag TNPs for colorimetric sensing of iodide with the detection limit down to 8.8 nM.[133] Li *et al.* found that the cysteine could inhibit the etching to Ag TNPs from I^-, and then extended the mechanism of anti–etching for the colorimetric detection of cysteine.

LOD for cysteine detection was down to 25 nM by the naked eye.[128]

■ CONCLUSIONS AND FUTURE PERSPECTIVES

The integration of various plasmonic nanomaterials to a variety of biological milieus, addressing their tunable nanostructures and optical properties, facile modification as well as biocompatibility, and so forth have been widely covered in the literature. Above we have elaborately discussed the recent efforts to construct plasmonic nanoparticles-based colorimetric assay systems for the ultrasensitive sensing of various analytes. Significantly, we reviewed two typical different strategies of colorimetric plasmon nanosensors, ie., inter-particle distance-dependent assay and plasmonic nanoparticles' size/morphology-dependent assay. Compared to traditional colorimetric assays with organic chromophores, each of these plasmon-based assays shows remarkable advantages, especially the highly sensitivity in response to external stimuli. We here highlight how, mainly over the past five years, scientists have demonstrated increasingly impressive examples of tailored plasmonic nanosensors by engineering the assembly or reconfiguration (growth/etching) of size- and shape-controlled nanoparticles for molecular detection. Despite the significant progress in fabricating nanoplasmonic platforms and developing their colorimetric applications as summarized above, several aspects related to current and future practical applications in molecular diagnostics still need to be addressed. Below, we intend to detail some of scientific research directions in this field, which are expected to redefine the plasmon-based colorimetric sensing assay in the near future.

At a fundamental level, the future development of such colorimetric assays resorts to the innovations in plasmonics-based optical responsibility and nanostructured materials.[3,10,134] Progress of material science has facilitated the plasmon-based colorimetric assay for the naked-eye detection of analytes at ever-lower levels, which in turn, has greatly contributed to their practical diagnostics. A rich library of stimulus-responsive plasmonic nanosystems can be used to fabricate the sensitive colorimetric sensors. Currently, gold/silver nanospheres and nanorods are the most widely used plasmonic nanomaterials in the colorimetric nanosensors, owing to their mature syntheses, facile surface modification, physicochemical stability as well as tunable optical properties. Although many other plasmonic nanostructures with varied chemical compositions (from aluminum to silver, gold) and different shapes (from spheres, rods to plates, stars) can be explored to fabricate plasmon-based colorimetric nanosensors, several alternative plasmonic nanomaterials beyond coinage metals have been predicted or even developed for plasmon-based colorimetric sensing use. As one example, we note that some of highly doped 2D materials–mainly for graphene and transition-metal oxides/chalogenides–exhibited tunable plasmon resonance peaks in the visible-near infrared region, which thereby expected to enable the highly sensitive plasmonic sensing of external targets.[135] Along with the rich plasmonic nanomaterials and collective optical properties, it is believe that the plasmon-based colorimetric nanosensors will continue to be of great benefit to the diverse sensing applications.

Motivated by the clinical and POC diagnostic applications, plasmon-based colorimetric sensing will undoubtedly undergo further improvements and refinements

in the future to meet the practical applications. First, the plasmonic nanomaterial-associated colorimetric assays normally have the common disadvantage of the less stability and reproducibility compared to traditional assays. Since the LSPR is markedly influenced not only by inter-particle distance, shapes and sizes of plasmonic nanostructures but also by the interface and surrounding mediums, the aggregate/dispersion state of plasmonic nanoprobe is susceptible to external stimulus in complicated environments, such as the existence of high salt and other interfering substrates Otherwise, because of the large surface area of nanomaterials, other impurities were usually non-specifically adsorbed during the sensing events, which leads to the false detection signals. Although specific surface chemistry using antifouling agents like bovine serum albumin and polyethylene glycol could resist surface fouling in practical use, there still remains many challenges.[136,137] For instance, polyethylene glycol molecules are subjective to be auto-oxidized in biological fluids and thereby unsatisfied for the long-term clinic uses.[42, 137] Reecently, some novle surface chemistries including the use of zwitterionic molecules have been developed, suggesting that they would be useful ways for issuing these problems in the plasmonic nanomaterials-associated colorimetric assays.[136]

High-throughput and ultrasensitive detection of biomolecules is critical for the development of plasmon-based colorimetric sensing in the diagnostic applications. Recent work suggests that combining fluidic devices (e.g. microfluidic chips) with plasmonic nanosensing system could dramatically improve the throughput capability for the parallel measurement of multiple targets in a single test, and also meet the

requirements of fluidic sample-based POC diagnostics.[138] For example, by integrating the AuNPs-based colorimetric sensors with a microfluidic chip, multiplexed POC detection could be achieved. In addition, molecular amplification in plasmon-based colorimetric sensing applications can now be achieved through many different strategies, whereas simple and general amplification strategies are still in high demand. In addition to this point of view, a reliable and robust strategy to amplify the plasmon-based colorimetric sensing signal is essential for the detection of trace biomarkers at the clinical level.

Another serious concern is how to quantitatively detect with personalized equipment (e.g. smartphones, wearable devices) and transfer the technique into the clinic, which will be the future goal for plasmon-based colorimetric diagnostics.[139,140] For examples, the imaging of AuNP solution can be done with a personalized smartphone and then processed to digital information, thereby realizing the quantitatively analysis of the analytes. It is expected to extend this concept into many other plasmon-based colorimetric sensing platforms. Otherwise, most of current plasmon-based colorimetric sensing systems are merely proof-of-concept demonstrations and remain challenging in the clinic. So as to accelerate clinical translation from this field research, it is essential to collaborate with front-line medical step for academic field.[4,16]

Over all, as an analytical technique, the plasmon-based colorimetric sensing system exhibit significant advantages and are challenging the traditional colorimetric assay. The preliminary achievements made by plasmon-based colorimetric nanosensors in

the past decade are promising, but have not been fully explored. Give the future of such assay related to POC/clinical diagnostics, there is still a need to focus on the fundamental research and their clinical translation, with the integration of advanced nanotechnology, biotechnology and other emerging technologies such as microfluidic chip, personalized equipment, etc..

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jhli@tsinghua.edu.cn.

Notes

The author declares no competing financial interest.

■ VOCABULARY

colorimetric analysis, an analytical technique for the quantitative detection of the colored compounds using the human color perception; surface plasmon resonance, the resonant oscillation of free conduction electrons stimulated by incident light; plasmonic nanoparticles, nano-sized particles whose electron density can couple with electromagnetic radiation of wavelengths; molecular diagnostics, a collection of techniques used to analyze biological markers; biosensor, an analytical device that combines a biological component with a physicochemical detector.

■ ABBREVIATIONS

ELISA, enzyme–linked immunosorbent assay; PCR, polymerase chain reaction; SPR, surface plasmon resonance; LSPR localized surface plasmon resonance; PSPR, propagating surface plasmon resonance;AuNPs, gold nanoparticles; AgNPs, silver nanoparticles; AuNRs, gold nanorods; silver TNPs, silver triangular nanoplates; NSs, nanoshells; CuO, copper monoxide; AuNCs, gold nanoclusters; nM, nanomolar; fM, femtomolar; aM, attomolar; zM, zeptomoles; POC, point–of–care; 3D, three-dimensional; NIR, near–infrared; GOx glucose oxidase; AChE,

acetylcholinesterase; ATC, acetylthiocholine; EV71, enterovirus 71; HFMD, hand, foot, and mouth disease; ChE, cholinesterase; OPs, organophosphate pesticides; *T. Pallidum, Treponema pallidum*; *S. Typhimurium, Salmonella typhimurium*; *L. Monocytogenes, Listeria monocytogenes; E. coli, Escherichia coli;* CuAAC, Cu(I)-catalyzed 1, 3-dipolar cycloaddition of azides and alkynes; ALP, akaline phosphatase; MP, Mycoplasma pneumonia; MNAzyme, multicomponent nucleic acid enzymes; KRAS, Kirsten rat sarcoma viral oncogene homologue; Con A, concanavalin A; H_2O_2, hydrogen peroxide; CEA, Carcinoembryonic antige; ALP, alkaline phosphatase; HBsAg, hepatitis B surface antigen; PSA, prostate specific antigen; MT, methyltestosterone; ADH, alcohol dehydrogenase; AFP, α–fetoprotein; ATCh, acetylcholine; DO, dissolved oxygen

■ ACKNOWLEDGMENT

This work was financially supported by National Natural Science Foundation of China (No. 61405076, No. 21621003, No. 21327806), the Fundamental Research Funds for the Central University (No. 2016QNA5001), and National Key Research and Development Program of China (No. 2016YFA0203101).

■ REFERENCES

(1) Saha, K.; Agasti, S. S.; Kim, C.; Li, X.; Rotello, V. M.: Gold Nanoparticles in Chemical and Biological Sensing. *Chemical Reviews* **2012**, *112*, 2739-2779.

(2) Howes, P. D.; Rana, S.; Stevens, M. M.: Plasmonic nanomaterials for biodiagnostics. *Chemical Society Reviews* **2014**, *43*, 3835-3853.

(3) Lim, W. Q.; Gao, Z. Q.: Plasmonic nanoparticles in biomedicine. *Nano Today* **2016**, *11*, 168-188.

(4) Song, Y. J.; Huang, Y. Y.; Liu, X. W.; Zhang, X. J.; Ferrari, M.; Qin, L. D.: Point-of-care technologies for molecular diagnostics using a drop of blood. *Trends in Biotechnology* **2014**, *32*, 132-139.

(5) Yang, X. L.; Tang, Y. A.; Alt, R. R.; Xie, X. Y.; Li, F.: Emerging techniques for ultrasensitive protein analysis. *Analyst* **2016**, *141*, 3473-3481.

(6) Zhou, W.; Gao, X.; Liu, D. B.; Chen, X. Y.: Gold Nanoparticles for In Vitro Diagnostics. *Chemical Reviews* **2015**, *115*, 10575-10636.

(7) Granger, J. H.; Schlotter, N. E.; Crawford, A. C.; Porter, M. D.: Prospects for point-of-care pathogen diagnostics using surface-enhanced Raman scattering (SERS). *Chemical Society Reviews* **2016**, *45*, 3865-3882.

(8) Wu, L.; Qu, X. G.: Cancer biomarker detection: recent achievements and challenges. *Chemical Society Reviews* **2015**, *44*, 2963-2997.

(9) Paterson, S.; de la Rica, R.: Solution-based nanosensors for in-field detection with the naked eye. *Analyst* **2015**, *140*, 3308-3317.

(10) Zheng, W. S.; Jiang, X. Y.: Integration of nanomaterials for colorimetric immunoassays with improved performance: a functional perspective. *Analyst* **2016**, *141*, 1196-1208.

(11) Wang, M.; Sun, C.;Wang, L.; Ji, X.; Bai, Y.; Li, T.; Li, J. Electrochemical detection of DNA immobilized on gold colloid particles modified self-assembled monolayer electrode with silver nanoparticle label, *J. Pharmaceutical and Biomedical Analysis*, **2003**, *33*, 1117-1125

(12) Zhang, Y.; Guo, Y. M.; Xianyu, Y. L.; Chen, W. W.; Zhao, Y. Y.; Jiang, X. Y.: Nanomaterials for Ultrasensitive Protein Detection. *Advanced Materials* **2013**, *25*, 3802-3819.

(13) Chen, Y. P.; Xianyu, Y. L.; Wu, J.; Yin, B. F.; Jiang, X. Y.: Click Chemistry-Mediated Nanosensors for Biochemical Assays. *Theranostics* **2016**, *6*, 969-985.

(14) Song, Y.; Wei, W.; Qu, X.: Colorimetric Biosensing Using Smart Materials. *Advanced Materials* **2011**, *23*, 4215-4236.

(15) Wu, Y.; Wang, D.; Li, Y.: Understanding of the major reactions in solution synthesis of functional nanomaterials. *Science China Materials* **2016**, *59*, 938-996.

(16) Giner-Casares, J. J.; Henriksen-Lacey, M.; Coronado-Puchau, M.; Liz-Marzan, L. M.: Inorganic nanoparticles for biomedicine: where materials scientists meet medical research. *Materials Today* **2016**, *19*, 19-28.

(17) Duan, J.; Zhan, J.: Recent developments on nanomaterials-based optical sensors for Hg^{2+} detection. *Science China Materials* **2015**, *58*, 223-240.

(18) Passarelli, N.; Perez, L. A.; Coronado, E. A.: Plasmonic Interactions: From Molecular Plasmonics and Fano Resonances to Ferroplasmons. *ACS Nano* **2014**, *8*, 9723-9728.

(19) Elghanian, R.; Storhoff, J. J.; Mucic, R. C.; Letsinger, R. L.; Mirkin, C. A.: Selective Colorimetric Detection of Polynucleotides Based on the Distance-Dependent Optical Properties of

Gold Nanoparticles. *Science* **1997**, *277*, 1078-1081.

(20) Hu, J.; Wang, Z.; Li, J.; Gold nanoparticles with special shapes: controlled synthesis, surface-enhanced Raman scattering, and the application in biodetection, *Sensors*, **2007**, *7*, 3299-3311.

(21) Verma, M. S.; Rogowski, J. L.; Jones, L.; Gu, F. X.: Colorimetric biosensing of pathogens using gold nanoparticles. *Biotechnology Advances* **2015**, *33*, 666-680.

(22) Kumar, A.; Kim, S.; Nam, J.-M.: Plasmonically Engineered Nanoprobes for Biomedical Applications. *Journal of the American Chemical Society* **2016**, *138*, 14509-14525.

(23) Kelly, K. L.; Coronado, E.; Zhao, L. L.; Schatz, G. C. The Optical Properties of Metal Nanoparticles: The Influence of Size, Shape, and Dielectric Environment. *J. Phys. Chem. B* **2003**, *107*, 668-677

(24) Tokel, O.; Inci, F.; Demirci, U.: Advances in Plasmonic Technologies for Point of Care Applications. *Chemical Reviews* **2014**, *114*, 5728-5752

(25) Wang, S.; Shan, X.; Pate, U.; Huang, X.; Lu, J.; Li, J.; Tao, N. Label-free imaging, detection and mass measurement of single viruses by Surface Plasmon Resonance, *Proc. National Acad. Sci.*, **2010**, *107*, 16028-16032

(26) Masson, J.-F.: Surface Plasmon Resonance Clinical Biosensors for Medical Diagnostics. *ACS Sensors* **2017**, *2*, 16-30.

(27) Peng, C. F.; Duan, X. H.; Khamba, G. W.; Xie, Z. J.: Highly sensitive "signal on" plasmonic ELISA for small molecules by the naked eye. *Analytical Methods* **2014**, *6*, 9616-9621.

(28) Boles, M. A.; Engel, M.; Talapin, D. V.: Self-Assembly of Colloidal Nanocrystals: From Intricate Structures to Functional Materials. *Chemical Reviews* **2016**, *116*, 11220-11289.

(29) Borges, J.; Mano, J. F.: Molecular Interactions Driving the Layer-by-Layer Assembly of Multilayers. *Chemical Reviews* **2014**, *114*, 8883-8942.

(30) Jones, M. R.; Osberg, K. D.; Macfarlane, R. J.; Langille, M. R.; Mirkin, C. A.: Templated Techniques for the Synthesis and Assembly of Plasmonic Nanostructures. *Chemical Reviews* **2011**, *111*, 3736-3827.

(31) Vogel, N.; Retsch, M.; Fustin, C. A.; del Campo, A.; Jonas, U.: Advances in Colloidal Assembly: The Design of Structure and Hierarchy in Two and Three Dimensions. *Chemical Reviews* **2015**, *115*, 6265-6311.

(32) Walther, A.; Muller, A. H. E.: Janus Particles: Synthesis, Self-Assembly, Physical Properties, and Applications. *Chemical Reviews* **2013**, *113*, 5194-5261.

(33) Valentini, P.; Fiammengo, R.; Sabella, S.; Gariboldi, M.; Maiorano, G.; Cingolani, R.; Pompa, P. P.: Gold-Nanoparticle-Based Colorimetric Discrimination of Cancer-Related Point Mutations with Picomolar Sensitivity. *ACS Nano* **2013**, *7*, 5530-5538.

(34) Xianyu, Y. L.; Wang, Z.; Jiang, X. Y.: A Plasmonic Nanosensor for Immunoassay via Enzyme-Triggered Click Chemistry. *ACS Nano* **2014**, *8*, 12741-12747.

(35) Xianyu, Y. L.; Chen, Y. P.; Jiang, X. Y.: Horseradish Peroxidase-Mediated, Iodide-Catalyzed Cascade Reaction for Plasmonic Immunoassays. *Analytical Chemistry* **2015**, *87*, 10688-10692.

(36) Liu, D. B.; Wang, Z. T.; Jin, A.; Huang, X. L.; Sun, X. L.; Wang, F.; Yan, Q.; Ge, S. X.; Xia, N. S.; Niu, G.; Liu, G.; Walker, A. R. H.; Chen, X. Y.: Acetylcholinesterase-Catalyzed Hydrolysis Allows Ultrasensitive Detection of Pathogens with the Naked Eye. *Angewandte Chemie-International Edition* **2013**, *52*, 14065-14069.

(37) Valentini, P.; Pompa, P. P.: A Universal Polymerase Chain Reaction Developer. *Angewandte Chemie-International Edition* **2016**, *55*, 2157-2160.

(38) Nie, X. M.; Huang, R.; Dong, C. X.; Tang, L. J.; Gui, R.; Jiang, J. H.: Plasmonic ELISA for the ultrasensitive detection of Treponema pallidum. *Biosensors & Bioelectronics* **2014**, *58*, 314-319.

(39) Wang, F. F.; Liu, S. Z.; Lin, M. X.; Chen, X.; Lin, S. R.; Du, X. Z.; Li, H.; Ye, H. B.; Qiu, B.; Lin, Z. Y.; Guo, L. H.; Chen, G. N.: Colorimetric detection of microcystin-LR based on disassembly of orient-aggregated gold nanoparticle dimers. *Biosensors & Bioelectronics* **2015**, *68*, 475-480.

(40) Wei, L. M.; Wang, X. Y.; Li, C.; Li, X. X.; Yin, Y. M.; Li, G. X.: Colorimetric assay for protein detection based on "nano-pumpkin" induced aggregation of peptide-decorated gold nanoparticles. *Biosensors & Bioelectronics* **2015**, *71*, 348-352.

(41) Chandrawati, R.; Stevens, M. M.: Controlled assembly of peptide-functionalized gold nanoparticles for label-free detection of blood coagulation Factor XIII activity. *Chemical Communications* **2014**, *50*, 5431-5434.

(42) Wu, S. J.; Tan, S. Y.; Ang, C. Y.; Luo, Z.; Zhao, Y. L.: Oxidation-triggered aggregation of gold nanoparticles for naked-eye detection of hydrogen peroxide. *Chemical Communications* **2016**, *52*, 3508-3511.

(43) Richards, S. J.; Fullam, E.; Besra, G. S.; Gibson, M. I.: Discrimination between bacterial phenotypes using glyco-nanoparticles and the impact of polymer coating on detection readouts. *Journal of Materials Chemistry B* **2014**, *2*, 1490-1498.

(44) Guo, L.; Xu, Y.; Ferhan, A. R.; Chen, G.; Kim, D.-H.: Oriented Gold Nanoparticle Aggregation for Colorimetric Sensors with Surprisingly High Analytical Figures of Merit. *Journal of the American Chemical Society* **2013**, *135*, 12338-12345.

(45) Bui, M. P. N.; Ahmed, S.; Abbas, A.: Single-Digit Pathogen and Attomolar Detection with the Naked Eye Using Liposome-Amplified Plasmonic Immunoassay. *Nano Letters* **2015**, *15*, 6239-6246.

(46) Gormley, A. J.; Chapman, R.; Stevens, M. M.: Polymerization Amplified Detection for Nanoparticle-Based Biosensing. *Nano Letters* **2014**, *14*, 6368-6373.

(47) Aili, D.; Selegard, R.; Baltzer, L.; Enander, K.; Liedberg, B.: Colorimetric Protein Sensing by Controlled Assembly of Gold Nanoparticles Functionalized with Synthetic Receptors. *Small* **2009**, *5*, 2445-2452.

(48) Lu, C.-H.; Wang, Y.-W.; Ye, S.-L.; Chen, G.-N.; Yang, H.-H.: Ultrasensitive detection of Cu2+ with the naked eye and application in immunoassays. *NPG Asia Mater* **2012**, *4*, e10.

(49) Acres, R. G.; Feyer, V.; Tsud, N.; Carlino, E.; Prince, K. C.: Mechanisms of Aggregation of Cysteine Functionalized Gold Nanoparticles. *The Journal of Physical Chemistry C* **2014**, *118*, 10481-10487.

(50) Wang, F.; Liu, X.; Lu, C.-H.; Willner, I.: Cysteine-Mediated Aggregation of Au Nanoparticles: The Development of a H_2O_2 Sensor and Oxidase-Based Biosensors. *ACS Nano* **2013**, *7*, 7278-7286.

(51) Liu, D.; Chen, W.; Tian, Y.; He, S.; Zheng, W.; Sun, J.; Wang, Z.; Jiang, X.: A Highly Sensitive Gold-Nanoparticle-Based Assay for Acetylcholinesterase in Cerebrospinal Fluid of Transgenic Mice with Alzheimer's Disease. *Advanced Healthcare Materials* **2012**, *1*, 90-95.

(52) Lu, L.; Xia, Y.: Enzymatic Reaction Modulated Gold Nanorod End-to-End Self-Assembly for Ultrahigh Sensitively Colorimetric Sensing of Cholinesterase and Organophosphate Pesticides in Human Blood. *Analytical Chemistry* **2015**, *87*, 8584-8591.

(53) Qu, W.; Liu, Y.; Liu, D.; Wang, Z.; Jiang, X.: Copper-Mediated Amplification Allows Readout of Immunoassays by the Naked Eye. *Angewandte Chemie-International Edition* **2011**, *123*,

3504-3507.

(54) Marti, A.; Costero, A. M.; Gavina, P.; Parra, M.: Selective colorimetric NO(g) detection based on the use of modified gold nanoparticles using click chemistry. *Chemical Communications* **2015**, *51*, 3077-3079.

(55) Zhang, Y.; Li, B.; Xu, C.: Visual detection of ascorbic acid via alkyne-azide click reaction using gold nanoparticles as a colorimetric probe. *Analyst* **2010**, *135*, 1579-1584.

(56) Song, J.; Cheng, L.; Liu, A.; Yin, J.; Kuang, M.; Duan, H.: Plasmonic Vesicles of Amphiphilic Gold Nanocrystals: Self-Assembly and External-Stimuli-Triggered Destruction. *Journal of the American Chemical Society* **2011**, *133*, 10760-10763.

(57) He, J.; Huang, X.; Li, Y.-C.; Liu, Y.; Babu, T.; Aronova, M. A.; Wang, S.; Lu, Z.; Chen, X.; Nie, Z.: Self-Assembly of Amphiphilic Plasmonic Micelle-Like Nanoparticles in Selective Solvents. *Journal of the American Chemical Society* **2013**, *135*, 7974-7984.

(58) Song, J.; Huang, P.; Duan, H.; Chen, X.: Plasmonic Vesicles of Amphiphilic Nanocrystals: Optically Active Multifunctional Platform for Cancer Diagnosis and Therapy. *Accounts of Chemical Research* **2015**, *48*, 2506-2515.

(59) Lin, Y.-Z.; Chang, P.-L.: Colorimetric Determination of DNA Methylation Based on the Strength of the Hydrophobic Interactions between DNA and Gold Nanoparticles. *ACS Applied Materials & Interfaces* **2013**, *5*, 12045-12051.

(60) Liu, J.; Cao, Z.; Lu, Y.: Functional Nucleic Acid Sensors. *Chemical Reviews* **2009**, *109*, 1948-1998.

(61) Kato, D.; Oishi, M.: Ultrasensitive Detection of DNA and RNA Based on Enzyme-Free Click Chemical Ligation Chain Reaction on Dispersed Gold Nanoparticles. *ACS Nano* **2014**, *8*, 9988-9997.

(62) Wang, J.; Wang, L.; Liu, X.; Liang, Z.; Song, S.; Li, W.; Li, G.; Fan, C.: A Gold Nanoparticle-Based Aptamer Target Binding Readout for ATP Assay. *Advanced Materials* **2007**, *19*, 3943-3946.

(63) Zagorovsky, K.; Chan, W. C. W.: A Plasmonic DNAzyme Strategy for Point-of-Care Genetic Detection of Infectious Pathogens. *Angewandte Chemie International Edition* **2013**, *52*, 3168-3171.

(64) Shen, W.; Deng, H.; Gao, Z.: Gold Nanoparticle-Enabled Real-Time Ligation Chain Reaction for Ultrasensitive Detection of DNA. *Journal of the American Chemical Society* **2012**, *134*, 14678-14681.

(65) Aslan, K.; Lakowicz, J. R.; Geddes, C. D.: Nanogold Plasmon Resonance-Based Glucose Sensing. 2. Wavelength-Ratiometric Resonance Light Scattering. *Analytical Chemistry* **2005**, *77*, 2007-2014.

(66) Otsuka, H.; Akiyama, Y.; Nagasaki, Y.; Kataoka, K.: Quantitative and Reversible Lectin-Induced Association of Gold Nanoparticles Modified with α-Lactosyl-ω-mercapto-poly(ethylene glycol). *Journal of the American Chemical Society* **2001**, *123*, 8226-8230.

(67) Tsai, C.-S.; Yu, T.-B.; Chen, C.-T.: Gold nanoparticle-based competitive colorimetric assay for detection of protein-protein interactions. *Chemical Communications* **2005**, 4273-4275.

(68) Otten, L.; Richards, S.-J.; Fullam, E.; Besra, G. S.; Gibson, M. I.: Gold nanoparticle-linked analysis of carbohydrate-protein interactions, and polymeric inhibitors, using unlabelled proteins; easy measurements using a 'simple' digital camera. *Journal of Materials Chemistry B* **2013**, *1*, 2665-2672.

(69) Reynolds, A. J.; Haines, A. H.; Russell, D. A.: Gold Glyconanoparticles for Mimics and

Measurement of Metal Ion-Mediated Carbohydrate−Carbohydrate Interactions. *Langmuir* **2006**, *22*, 1156-1163.

(70) Schofield, C. L.; Field, R. A.; Russell, D. A.: Glyconanoparticles for the Colorimetric Detection of Cholera Toxin. *Analytical Chemistry* **2007**, *79*, 1356-1361.

(71) Niikura, K.; Nagakawa, K.; Ohtake, N.; Suzuki, T.; Matsuo, Y.; Sawa, H.; Ijiro, K.: Gold Nanoparticle Arrangement on Viral Particles through Carbohydrate Recognition: A Non-Cross-Linking Approach to Optical Virus Detection. *Bioconjugate Chemistry* **2009**, *20*, 1848-1852.

(72) Wen, D.; Liu, W.; Herrmann, A.-K.; Haubold, D.; Holzschuh, M.; Simon, F.; Eychmüller, A.: Simple and Sensitive Colorimetric Detection of Dopamine Based on Assembly of Cyclodextrin-Modified Au Nanoparticles. *Small* **2016**, *12*, 2439-2442.

(73) Lin, S.-Y.; Liu, S.-W.; Lin, C.-M.; Chen, C. H.: Recognition of Potassium Ion in Water by 15-Crown-5 Functionalized Gold Nanoparticles. *Analytical Chemistry* **2002**, *74*, 330-335.

(74) Kim, Y.; Johnson, R. C.; Hupp, J. T.: Gold Nanoparticle-Based Sensing of "Spectroscopically Silent" Heavy Metal Ions. *Nano Letters* **2001**, *1*, 165-167.

(75) Obare, S. O.; Hollowell, R. E.; Murphy, C. J.: Sensing Strategy for Lithium Ion Based on Gold Nanoparticles. *Langmuir* **2002**, *18*, 10407-10410.

(76) Zhao, Q.; Huang, H. W.; Zhang, L. Y.; Wang, L. Q.; Zeng, Y. L.; Xia, X. D.; Liu, F. P.; Chen, Y.: Strategy To Fabricate Naked-Eye Readout Ultrasensitive Plasmonic Nanosensor Based on Enzyme Mimetic Gold Nanoclusters. *Analytical Chemistry* **2016**, *88*, 1412-1418.

(77) Keunen, R.; Macoretta, D.; Cathcart, N.; Kitaev, V.: Stable ligand-free stellated polyhedral gold nanoparticles for sensitive plasmonic detection. *Nanoscale* **2016**, *8*, 2575-2583.

(78) Zhou, Y. J.; He, K. Y.; Liu, S. Q.; Li, Y.; Nie, Z.; Huang, Y.; Yao, S. Z.: Chemical colorimetric square wave and its derived logic gates based on tunable growth of plasmonic gold nanoparticles. *RSCAdvances* **2014**, *4*, 18668-18675.

(79) Liu, H. Q.; Rong, P. F.; Jia, H. W.; Yang, J.; Dong, B.; Dong, Q.; Yang, C. J.; Hu, P. Z.; Wang, W.; Liu, H. T.; Liu, D. B.: A Wash-Free Homogeneous Colorimetric Immunoassay Method. *Theranostics* **2016**, *6*, 54-64.

(80) Luo, W.; Zhu, C.; Su, S.; Li, D.; He, Y.; Huang, Q.; Fan, C.: Self-catalyzed, self-limiting growth of glucose oxidase-mimicking gold nanoparticles. *ACS Nano* **2010**, *4*, 7451-8.

(81) O'Connor, E. F.; Paterson, S.; Rica, R. D. L.: Naked-eye detection as a universal approach to lower the limit of detection of enzyme-linked immunoassays. *Analytical and Bioanalytical Chemistry* **2016**, *408*, 1-5.

(82) Liu, D.; Yang, J.; Wang, H. F.; Wang, Z.; Huang, X.; Wang, Z.; Niu, G.; Walker, A. R. H.; Chen, X.: Glucose Oxidase-Catalyzed Growth of Gold Nanoparticles Enables Quantitative Detection of Attomolar Cancer Biomarkers. *Analytical Chemistry* **2014**, *86*, 5800-6.

(83) Yan, J.; Wang, L. D.; Tang, L. H.; Lin, L.; Liu, Y.; Li, J. H.: Enzyme-guided plasmonic biosensor based on dual-functional nanohybrid for sensitive detection of thrombin. *Biosensors & Bioelectronics* **2015**, *70*, 404-410.

(84) Xiong, Y. M.; Zhang, Y. Y.; Rong, P. F.; Yang, J.; Wang, W.; Liu, D. B.: A high-throughput colorimetric assay for glucose detection based on glucose oxidase-catalyzed enlargement of gold nanoparticles. *Nanoscale* **2015**, *7*, 15584-15588.

(85) Rodríguez-Lorenzo, L.; de la Rica, R.; Álvarez-Puebla, R. A.; Liz-Marzán, L. M.; Stevens, M. M.: Plasmonic nanosensors with inverse sensitivity by means of enzyme-guided crystal growth. *Nature Materials* **2012**, *11*, 604-607.

(86) Chen, R.; Huang, X. L.; Xu, H. Y.; Xiong, Y. H.; Li, Y. B.: Plasmonic Enzyme-Linked Immunosorbent Assay Using Nanospherical Brushes as a Catalase Container for Colorimetric Detection of Ultralow Concentrations of Listeria monocytogenes. *Acs Applied Materials & Interfaces* **2015**, *7*, 28632-28639.

(87) Li, Y. Y.; Ma, X. M.; Xu, Z. M.; Liu, M. H.; Lin, Z. Y.; Qiu, B.; Guo, L. H.; Chen, G. N.: Multicolor ELISA based on alkaline phosphatase-triggered growth of Au nanorods. *Analyst* **2016**, *141*, 2970-2976.

(88) Peng, M. P.; Ma, W.; Long, Y. T.: Alcohol Dehydrogenase-Catalyzed Gold Nanoparticle Seed-Mediated Growth Allows Reliable Detection of Disease Biomarkers with the Naked Eye. *Analytical Chemistry* **2015**, *87*, 5891-5896.

(89) Zhou, C. H.; Zhao, J. Y.; Pang, D. W.; Zhang, Z. L.: Enzyme-Induced Metallization as a Signal Amplification Strategy for Highly Sensitive Colorimetric Detection of Avian Influenza Virus Particles. *Analytical Chemistry* **2014**, *86*, 2752-2759.

(90) Zhu, C. Q.; Hong, Y.; Xiao, Z.; Zhou, Y.; Jiang, Y.; Huang, M.; Xu, X. L.; Zhou, G. H.: Colorimetric determination of Salmonella typhimurium based on aptamer recognition. *Analytical Methods* **2016**, *8*, 6560-6565.

(91) Guo, Y. H.; Wu, J.; Li, J.; Ju, H. X.: A plasmonic colorimetric strategy for biosensing through enzyme guided growth of silver nanoparticles on gold nanostars. *Biosensors & Bioelectronics* **2016**, *78*, 267-273.

(92) Wang, S.; Bi, S.; Wang, Z. H.; Xia, J. F.; Zhang, F. F.; Yang, M.; Gui, R. J.; Li, Y. H.; Xia, Y. Z.: A plasmonic aptasensor for ultrasensitive detection of thrombin via arrested rolling circle amplification. *Chemical Communications* **2015**, *51*, 7927-7930.

(93) Yang, X. J.; Gao, Z. Q.: Enzyme-catalysed deposition of ultrathin silver shells on gold nanorods: a universal and highly efficient signal amplification strategy for translating immunoassay into a litmus-type test. *Chemical Communications* **2015**, *51*, 6928-6931.

(94) Cecchin, D.; de la Rica, R.; Bain, R. E. S.; Finnis, M. W.; Stevens, M. M.; Battaglia, G.: Plasmonic ELISA for the detection of gp120 at ultralow concentrations with the naked eye. *Nanoscale* **2014**, *6*, 9559-9562.

(95) de la Rica, R.; Stevens, M. M.: Plasmonic ELISA for the ultrasensitive detection of disease biomarkers with the naked eye. *Nature Nanotechnology* **2012**, *7*, 821-824.

(96) Chen, F.; Lin, M. L.; Zhao, Y.; Zhao, Y. X.: Catalase-functionalized SiO_2 nanoparticles mediate growth of gold nanoparticles for plasmonic biosensing of attomolar microRNA with the naked eye. *RCS Advances* **2016**, *6*, 15709-15715.

(97) Gao, Z. Q.; Hou, L.; Xu, M. D.; Tang, D. P.: Enhanced Colorimetric Immunoassay Accompanying with Enzyme Cascade Amplification Strategy for Ultrasensitive Detection of Low-Abundance Protein. *Scientific Reports* **2014**, *4*, 3966

(98) de la Rica, R.; Stevens, M. M.: Plasmonic ELISA for the detection of analytes at ultralow concentrations with the naked eye. *Nature Protocols* **2013**, *8*, 1759-1764.

(99) Chen, F.; Lin, M. L.; Zhao, Y.; Zhao, Y. X.: Catalase-functionalized SiO_2 nanoparticles mediate growth of gold nanoparticles for plasmonic biosensing of attomolar microRNA with the naked eye. *RSC Advances* **2016**, *6*, 15709-15715.

(100) Fanjul-Bolado, P.; Hernández-Santos, D.; González-García, M. B.; Costa-García, A.: Alkaline Phosphatase-Catalyzed Silver Deposition for Electrochemical Detection. *Analytical Chemistry* **2007**, *79*, 5272-5277.

(101) Xiao, Y.; Pavlov, V.; Levine, S.; Niazov, T.; Markovitch, G.; Willner, I.: Catalytic Growth of Au Nanoparticles by NAD(P)H Cofactors: Optical Sensors for NAD(P)+-Dependent Biocatalyzed Transformations. *Angewandte Chemie International Edition* **2004**, *43*, 4519-4522.

(102) Tang, Y.; Zhang, W.; Liu, J.; Zhang, L.; Huang, W.; Huo, F. W.; Tian, D. B.: A plasmonic nanosensor for lipase activity based on enzyme-controlled gold nanoparticles growth in situ. *Nanoscale* **2015**, *7*, 6039-6044.

(103) Shlyahovsky, B.; Katz, E.; Xiao, Y.; Pavlov, V.; Willner, I.: Optical and Electrochemical Detection of NADH and of NAD+-Dependent Biocatalyzed Processes by the Catalytic Deposition of Copper on Gold Nanoparticles. *Small* **2005**, *1*, 213-216.

(104) Willner, I.; Baron, R.; Willner, B.: Growing Metal Nanoparticles by Enzymes. *Advanced Materials* **2006**, *18*, 1109-1120.

(105) Guo, Y.; Li, W.; Zheng, M.; Yi, H.: Facile Preparation of Graphene Dots Functionalized Au Nanoparticles and Their Application as Peroxidase Mimetics in Glucose Detection. *Acta Chimica Sinica* **2014**, *72*, 713-719.

(106) He, H.; Xu, X.; Wu, H.; Jin, Y.: Enzymatic Plasmonic Engineering of Ag/Au Bimetallic Nanoshells and Their Use for Sensitive Optical Glucose Sensing. *Advanced Materials* **2012**, *24*, 1736-1740.

(107) He, H. L.; Xu, X. L.; Wu, H. X.; Zhai, Y. J.; Jin, Y. D.: In Situ Nanoplasmonic Probing of Enzymatic Activity of Monolayer-Confined Glucose Oxidase on Colloidal Nanoparticles. *Analytical Chemistry* **2013**, *85*, 4546-4553.

(108) Xia, Y. S.; Ye, J. J.; Tan, K. H.; Wang, J. J.; Yang, G.: Colorimetric Visualization of Glucose at the Submicromole Level in Serum by a Homogenous Silver Nanoprism-Glucose Oxidase System. *Analytical Chemistry* **2013**, *85*, 6241-6247.

(109) Liang, J. J.; Yao, C. Z.; Li, X. Q.; Wu, Z.; Huang, C. H.; Fu, Q. Q.; Lan, C. F.; Cao, D. L.; Tang, Y.: Silver nanoprism etching-based plasmonic ELISA for the high sensitive detection of prostate-specific antigen. *Biosensors & Bioelectronics* **2015**, *69*, 128-134.

(110) Yang, X. J.; Yu, Y. B.; Gao, Z. Q.: A Highly Sensitive Plasmonic DNA Assay Based on Triangular Silver Nanoprism Etching. *ACS Nano* **2014**, *8*, 4902-4907.

(111)Yu, F.; Li, Y.; Li, M.; Tang, L.; He, J.-J.: DNAzyme-integrated plasmonic nanosensor for bacterial sample-to-answer detection. *Biosensors and Bioelectronics* **2017**, *89, Part 2*, 880-885.

(112) Alex, S. A.; Chandrasekaran, N.; Mukherjee, A.: State-of-the-art strategies for the colorimetric detection of heavy metals using gold nanorods based on aspect ratio reduction. *Analytical Methods* **2016**, *8*, 2131-2137.

(113) Mettela, G.; Kulkarni, G. U.: Facet selective etching of Au microcrystallites. *Nano Research* **2015**, *8*, 2925-2934.

(114) Chen, L.; Fu, X.; Lu, W.; Chen, L.: Highly Sensitive and Selective Colorimetric Sensing of Hg^{2+} Based on the Morphology Transition of Silver Nanoprisms. *ACS Applied Materials & Interfaces* **2013**, *5*, 284-290.

(115) Yang, R.; Song, D.; Wang, C.; Zhu, A.; Xiao, R.; Liu, J.; Long, F.: Etching of unmodified Au@Ag nanorods: a tunable colorimetric visualization for the rapid and high selective detection of Hg^{2+}. *RSC Advances* **2015**, *5*, 102542-102549.

(116) Liu, W.; Hou, S.; Yan, J.; Zhang, H.; Ji, Y.; Wu, X.: Quantification of proteins using enhanced etching of Ag coated Au nanorods by the Cu^{2+}/bicinchoninic acid pair with improved sensitivity. *Nanoscale* **2016**, *8*, 780-784.

(117) Zhu, J.; Yu, Y.-Q.; Li, J.-J.; Zhao, J.-W.: Colorimetric detection of lead(II) ions based on accelerating surface etching of gold nanorods to nanospheres: the effect of sodium thiosulfate. *RSC Advances* **2016**, *6*, 25611-25619.

(118) Wen, T.; Zhang, H.; Tang, X.; Chu, W.; Liu, W.; Ji, Y.; Hu, Z.; Hou, S.; Hu, X.; Wu, X.: Copper Ion Assisted Reshaping and Etching of Gold Nanorods: Mechanism Studies and Applications. *The Journal of Physical Chemistry C* **2013**, *117*, 25769-25777.

(119) Zhang, Z.; Chen, Z.; Qu, C.; Chen, L.: Highly Sensitive Visual Detection of Copper Ions Based on the Shape-Dependent LSPR Spectroscopy of Gold Nanorods. *Langmuir* **2014**, *30*, 3625-3630.

(120) Chen, Z.; Liu, R.; Wang, S.; Qu, C.; Chen, L.; Wang, Z.: Colorimetric sensing of copper(ii) based on catalytic etching of gold nanorods. *RSC Advances* **2013**, *3*, 13318-13323.

(121) Liu, J.-M.; Jiao, L.; Lin, L.-P.; Cui, M.-L.; Wang, X.-X.; Zhang, L.-H.; Zheng, Z.-Y.; Jiang, S.-L.: Non-aggregation based label free colorimetric sensor for the detection of Cu^{2+} based on catalyzing etching of gold nanorods by dissolve oxygen. *Talanta* **2013**, *117*, 425-430.

(122) Free, P.; Conger, G.; Wu, S.; Zhang, J. B.; Fernig, D. G.: High colloidal stability of gold nanorods coated with a peptide-ethylene glycol: Analysis by cyanide-mediated etching and nanoparticle tracking analysis. *Colloids and Surfaces B-Biointerfaces* **2016**, *146*, 871-878.

(123) Lee, S.; Nam, Y.-S.; Choi, S.-H.; Lee, Y.; Lee, K.-B.: Highly sensitive photometric determination of cyanide based on selective etching of gold nanorods. *Microchimica Acta* **2016**, *183*, 3035-3041.

(124) Koehler, F. M.; Raso, R. A.; Grass, R. N.; Stark, W. J.: beta-D-Glucosidase Assisted Gold Dissolution as Non-Optical and Quantifiable Detection Technique for Immunoassays. *Small* **2013**, *9*, 4000-4005.

(125) Zhang, Z.; Chen, Z.; Cheng, F.; Zhang, Y.; Chen, L.: Iodine-mediated etching of gold nanorods for plasmonic sensing of dissolved oxygen and salt iodine. *Analyst* **2016**, *141*, 2955-2961.

(126) Weng, G.; Dong, X.; Li, J.; Zhao, J.: Halide ions can trigger the oxidative etching of gold nanorods with the iodide ions being the most efficient. *Journal of Materials Science* **2016**, *51*, 7678-7690.

(127) Zhang, Z.; Chen, Z.; Chen, L.: Ultrasensitive Visual Sensing of Molybdate Based on Enzymatic-like Etching of Gold Nanorods. *Langmuir* **2015**, *31*, 9253-9259.

(128) Li, Y.; Li, Z.; Gao, Y.; Gong, A.; Zhang, Y.; Hosmane, N. S.; Shen, Z.; Wu, A.: "Red-to-blue" colorimetric detection of cysteine via anti-etching of silver nanoprisms. *Nanoscale* **2014**, *6*, 10631-10637.

(129) Zhong, Y.; Wang, Q.; He, Y.; Ge, Y.; Song, G.: A novel fluorescence and naked eye sensor for iodide in urine based on the iodide induced oxidative etching and aggregation of Cu nanoclusters. *Sensors and Actuators B-Chemical* **2015**, *209*, 147-153.

(130) Liu, J.-M.; Jiao, L.; Cui, M.-L.; Lin, L.-P.; Wang, X.-X.; Zheng, Z.-Y.; Zhang, L.-H.; Jiang, S.-L.: A highly sensitive non-aggregation colorimetric sensor for the determination of I^- based on its catalytic effect on Fe^{3+} etching gold nanorods. *Sensors and Actuators B: Chemical* **2013**, *188*, 644-650.

(131) Hsu, M.-S.; Cao, Y.-W.; Wang, H.-W.; Pan, Y.-S.; Lee, B.-H.; Huang, C.-L.: Time-Dependent Surface Plasmon Resonance Spectroscopy of Silver Nanoprisms in the Presence of Halide Ions. *ChemPhysChem* **2010**, *11*, 1742-1748.

(132) Jiang, X. C.; Yu, A. B.: Silver Nanoplates:

Inorganic Anions. *Langmuir* **2008**, *24*, 4300-4309.

(133) Yang, X.-H.; Ling, J.; Peng, J.; Cao, Q.-E.; Ding, Z.-T.; Bian, L.-C.: A colorimetric method for highly sensitive and accurate detection of iodide by finding the critical color in a color change process using silver triangular nanoplates. *Analytica Chimica Acta* **2013**, *798*, 74-81.

(134) Ding, S.-Y.; Yi, J.; Li, J.-F.; Ren, B.; Wu, D.-Y.; Panneerselvam, R.; Tian, Z.-Q.: Nanostructure-based plasmon-enhanced Raman spectroscopy for surface analysis of materials. *Nature Reviews Materials* **2016**, *1*, 16021.

(135) Liu, W.; Xu, Q.; Cui, W.; Zhu, C.; Qi, Y.: CO_2-Assisted Fabrication of Two-Dimensional Amorphous Molybdenum Oxide Nanosheets for Enhanced Plasmon Resonances. *Angewandte Chemie* **2017**, *129*, 1622-1626.

(136) Yan, C.; Yu, S.; Jiang, Y.; He, Q.; Heng, C.: Fabrication of Paper-based Microfluidic Devices by Plasma Treatment and Its Application in Glucose Determination. *Acta Chimica Sinica* **2014**, *72*, 1099-1104.

(137) Cui, M.; Wang, Y.; Jiao, M.X.; Jayachandran, S.; Wu, Y.; Fan, X.; Lu, X. Mixed Self-Assembled Aptamer and Newly Designed Zwitterionic Peptide as Antifouling Biosensing Interface for Electrochemical Detection of alpha-Fetoprotein, *ACS Sensors* **2017**, DOI:10.1021/acssensors.7b00103

(138) Callow, J. A.; Callow, M. E. Trends in the development of environmentally friendly fouling-resistant marine coatings. *Nature Communications* **2011**, *2*, 244.

(139) Wang, Y.; Liu, X.; Chen, P.; Tran, N. T.; Zhang, J.; Chia, W. S.; Boujday, S.; Liedberg, B.: Smartphone spectrometer for colorimetric biosensing. *Analyst* **2016**, *141*, 3233-3238.

(140) Roda, A.; Michelini, E.; Zangheri, M.; Fusco, M.; Calabria, D.; Simoni, P.: Smartphone-based biosensors: A critical review and perspectives. *TrAC Trends in Analytical Chemistry* **2016**, *79*, 317-325.

Table 1 Intermolecular Force Involved in Plasmonic Nanoparticles Aggregate for Plasmon-Based Colorimetric Nanosensors.

Driving force	Plasmonic nanoparticles	Signal amplification	Detection target	Linear range	Detection limit	ref
Electrostatic nteractions	Citrate-capped AuNPs	Enzyme-triggered polymerization	Iron/copper HRP Catalase,	2~50 ppb N.A N.A.	50 ppb 250ng/mL 0.7 ng/mL	46
	Citrate-capped AuNPs	AChE-catalyzed hydrolysis	T. pallidum antibodies	1 pg/mL~10 ng/mL	0.98 pg/mL	38
	Citrate-capped AuNPs	AChE-catalyzed hydrolysis	EV71 orCA16	10^4 –10^8 copies/mL	10^3 copies/mL	36
	Citrate-capped AuNPs	Cysteine loaded liposome	Live pathogen Rabbit IgG	N.A. N.A.	Single copy 17 aM	45
Covalent bonding	Citrate capped AuNPs	HRP-mediated, iodide-catalyzed reaction	Anti-HCV antibodies	N.A.	1 ng/mL	35
	Alkyne-modified AuNP	ALP-triggered click chemistry	Rabbit antihuman IgG	0.8 ~ 2000 ng/mL.	2 ng/mL	34
	Peptide-modified AuNPs	Enzyme-catalyzed covalent crosslinking	Factor XIII activity	N.A.	0.01 U mL	41
hydrophobic interaction	PEG-modified AuNPs	w.o.	H_2O_2	10~ 2000 mM	10 mM	42
	Polypeptide-functionalized AuNPs	w.o.	HCAII; Fab57	N.A.	10 nM; 25 nM	47
Biologically specific interactions	DNA-modified AuNPs	PCR	HIV-related DNA	N.A.	0.01 zeptomoles	37
	Aptamer-linked AuNPs	Orient-aggregation of AuNPs dimers	Microcystin-LR	0.1–250 nM	0.05 nM	39
	DNA-linked AuNPs	Orient-aggregation of AuNPs dimers	DNA	1.0 pM~10 nM	1.0 pM	44
	DNA-conjugated AuNPs	Isothermal amplification	DNA Point Mutations	N.A.	32 fmol	33
	1-Thiolglucose modified AuNPs	Glyco-chemical interactions	FimH positive bacteria	N.A.	1.5*107 CFU/mL□	43
Host−guest interactions	Peptide-modified AuNPs	CB[8]-aromatic group interaction	Flt-1	0.2 ~ 10 nM	0.2 nM	40

Table 2 Enzyme-Mediated Growth of Plasmonic Nanoparticles for Plasmon-Based Colorimetric Nanosensors.

Agents	Nanomaterials	Scheme/Mechanism	targets	Detection limit	ref
H_2O_2	AuNPs	$HAuCl_4 + H_2O_2 \xrightarrow{GNP} Au@GNP$	CA15-3 T3 Thyroid Hormone;	7.52×10^{-14} U/mL 2.0×10^{-15} mg/mL	76
NH_2OH	AuNPs	$HAuCl_4 + NH_2OH \xrightarrow{GNPs} Au@GNPs$	IgG CEA	3.74 ng/mL 5.66 ng/mL	79
Catalase	AuNPs	$2Au^{3+} + 3H_2O_2 \xrightarrow{GNP} 2Au@GNP + 3O_2 + 6H^+$ $2H_2O_2 \xrightarrow{Catalase} 2H_2O + O_2$	PSA	1×10^{-21} g/ml	85
			gp120	8×10^{-20} M	94
			Methyltestosterone	0.01 ng/mL	27
			Listeria monocytogenes	80 CFU/mL	86
			MicroRNA	0.1 pM	96
			S. typhimurium	10 cfu mL^{-1}	90
DNAzymes	AuNPs	$2Au^{3+} + 3H_2O_2 \xrightarrow{AuNP} 2Au^0 + 3O_2 + 6H^+$ $2H_2O_2 \xrightarrow{HRP\text{-}mimicking\ DNAzyme} 2H_2O + O_2$	thrombin,	10 aM	92
Glucose oxidase (GOx)	Ag@AuNPs	$Glucose + O_2 + H_2O \xrightarrow{GOx} Gluconic\ acid + H_2O_2$ $Ag^+ + H_2O_2 \xrightarrow{Growth} Ag@GNS$	PSA	10^{-18} g ml^{-1}	93
	5 nm AuNPs	$Glucose + O_2 + H_2O \xrightarrow{GOx} Gluconic\ acid + H_2O_2$ $HAuCl_4 + H_2O_2 \xrightarrow{Growth} Au@GNPs$	glucose	0.1 mM	84
	$Au@Fe_3O_4$ NPs		thrombin	500 pM	83

Alkaline phosphatase (ALP)	Pd@Au NSs	$\text{ascorbic acid 2-phosphate} \xrightarrow{\text{ALP}} \text{ascorbic acid}$ $H_2PdCl_6 + AA \xrightarrow{\text{AuNP}} \text{Au/PdNP}$ $TMB + H_2O_2 \xrightarrow{\text{Au/PdNP}} TMB_{ox}$	PSA	0.05 ng mL^{-1}	97
	AuNPs	$\text{p-Aminophenyl phosphate monohydrate} \xrightarrow{\text{ALP}} \text{p-aminophenol} + PO_4^{3-}$ $\text{p-aminophenol} + Ag^+ \xrightarrow{\text{AuNP}} \text{AuNP/Ag}$	Avian Influenza Virus Particles	12 fM	89
	AuNRs	$\text{ascorbic acid 2-phosphate} \xrightarrow{\text{ALP}} \text{4-aminophenol}$ $Ag^+ + \text{4-aminophenol} \xrightarrow{\text{AuNP}} \text{AuNR/Ag}$	PSA	10 pg ml^{-1}	93
	Ag/AuNSs	$\text{ascorbic acid 2-phosphate} \xrightarrow{\text{ALP}} \text{ascorbic acid}$ $Ag^+ + AA \xrightarrow{\text{AuNS}} \text{AuNS/Ag}$	DNA	2.6 fM	91
	AuNRs	$\text{ascorbic acid 2-phosphate} \xrightarrow{\text{ALP}} \text{ascorbic acid}$ $HAuCl_4 + AA \xrightarrow{\text{AuNP}} \text{AuNPs}$	PSA	3 fg mL^{-1}	87
Alcohol dehydrogenase (ADH)	AuNPs	$NAD^+ + \text{ethanol} \xrightarrow{\text{ADH}} NADH + \text{acetaldehyde}$ $HAuCl_4 + NADH \longrightarrow \text{AuNP}$	HBsAg	1 pg mL^{-1}	88

Figure 1

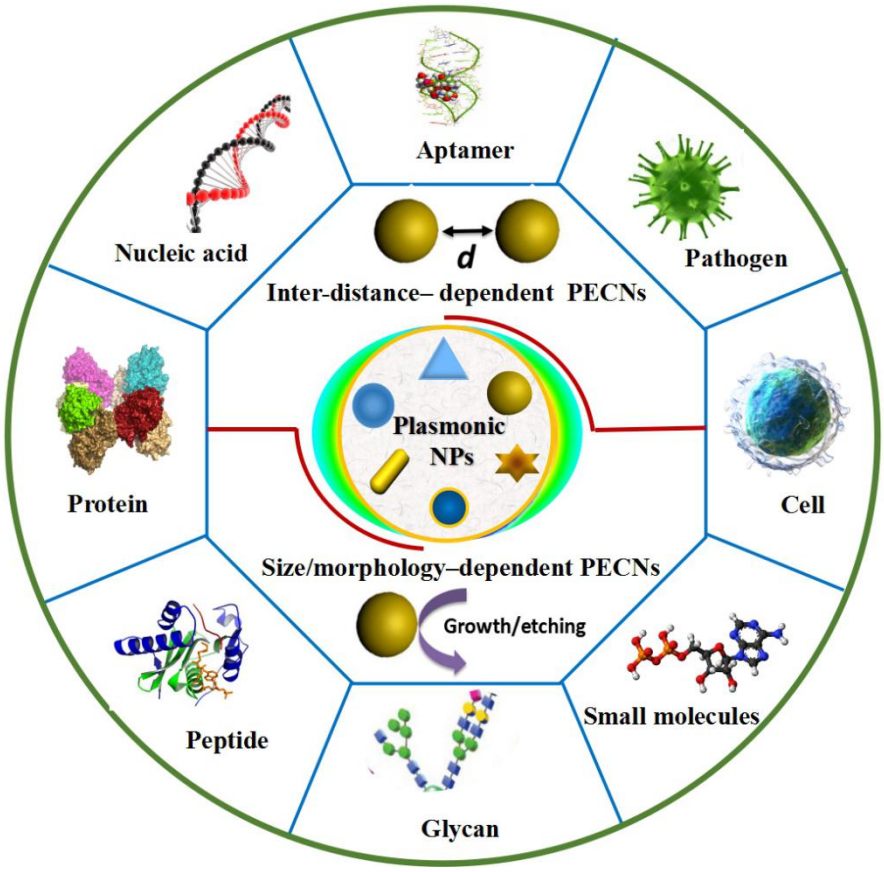


Figure 1. Schematic representation of colorimetric sensors with plasmonic nanoparticles, which are classified to two categories of inter-particle distance-dependent and size/morphology-dependent assays.

Figure 2

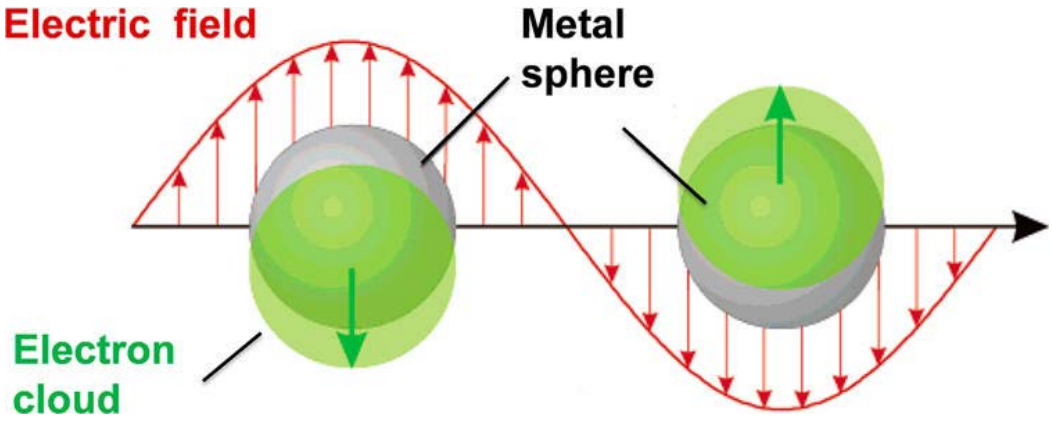


Figure 2. Schematic representation of a localized surface plasmon, in which coherent electrons oscillate around the nanoparticle surface under the electric field. Reprinted with Permission from ref 23. Copyright 2003 American Chemical Society

Figure 3

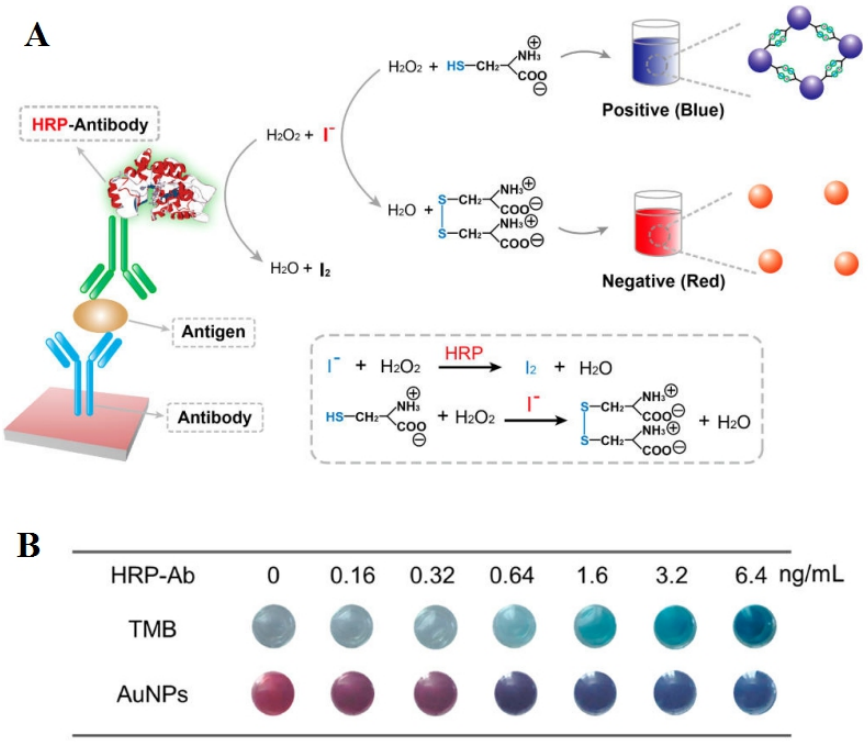


Figure 3. (A) Plasmonic immunoassay based on HRP-mediated modulation of AuNPs that enables naked-eye readout. In the presence of H_2O_2, HRP-catalyzed oxidation of iodide and iodide-catalyzed oxidation of cysteine can modulate the dispersion/aggregation of AuNPs. (B) A comparison of the color of solution between conventional TMB-based assay and AuNPs-based assay in the detection of HRP-conjugated antibody (HRP-Ab). Reprinted with Permission from ref 35. Copyright 2015 American Chemical Society.

Figure 4

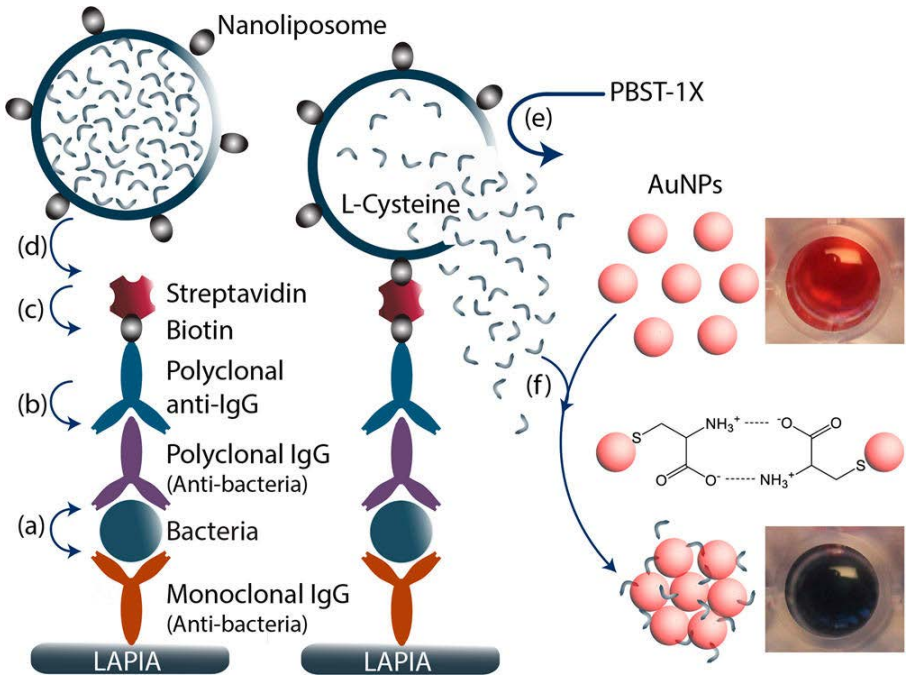


Figure 4. Schematic illustration of the liposome-amplified plasmonic immunoassay. One target could rapidly trigger a chemical cascade reaction leading to AuNPs aggregation, which includes different steps: a) Capture of the target (biomarker, pathogen, toxin) using sandwich immunoassay; b) After washing steps, biotinylated secondary antibody was allowed to interact with the immunocomplex; c) After incubation and washing, streptavidin was added to interact and bond to biotinylated IgG; d) After washing steps, biotin-conjugated liposomes containing cysteine were added to the medium followed by AuNPs solution; e) Addition of PBS-Tween-20 1× to the medium causes the breakdown of the liposomes and the release of cysteine, resulting in the immediate aggregation of AuNPs and color transition from red to dark-blue (f). Reprinted with Permission from ref 46. Copyright 2014 American Chemical Society.

Figure 5

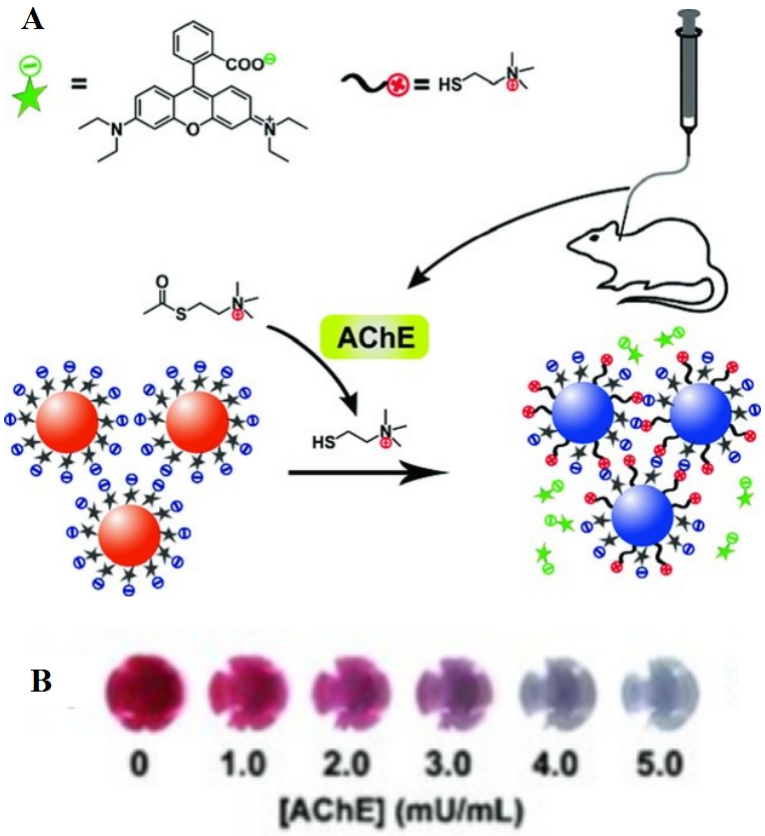


Figure 5. (A) The scheme of colorimetric and fluorometric detection of AChE using RB-capped AuNPs. In the presence of thiocholine, derived from the hydrolysis of ATC catalyzed by AChE, the well-dispersed RB-capped AuNP will be aggregated through electrostatic interaction, along with the fluorescence recovery of RB. (B) The color change of such assay for AChE in the presence of the different concentrations of AChE. Reprinted with Permission from ref 51. Copyright 2012 John Wiley and Sons.

Figure 6

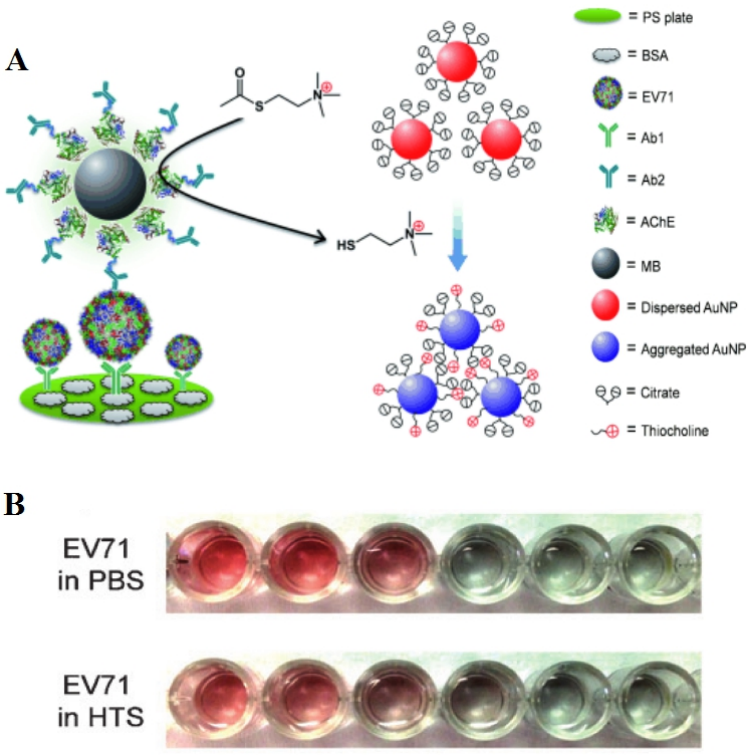


Figure 6. AChE-mediated AuNPs-based sandwich ELISA assay. (A) The scheme of used ELISA format. The target enterovirus 71 (EV71) is capture by the antibody (Ab1) onto polystyrene (PS) substrate and recognized by a AChE-conjugated detection antibody (Ab2) which is loaded onto the magnetic beads (MB). (B) Naked-eye detection of EV71 with concentration ranging from 10^4 to 10^8 copies mL^{-1} in phosphate buffered saline (PBS) and human throat swab (HTS). Reprinted with Permission from ref 36. Copyright 2013 John Wiley and Sons.

Figure 7

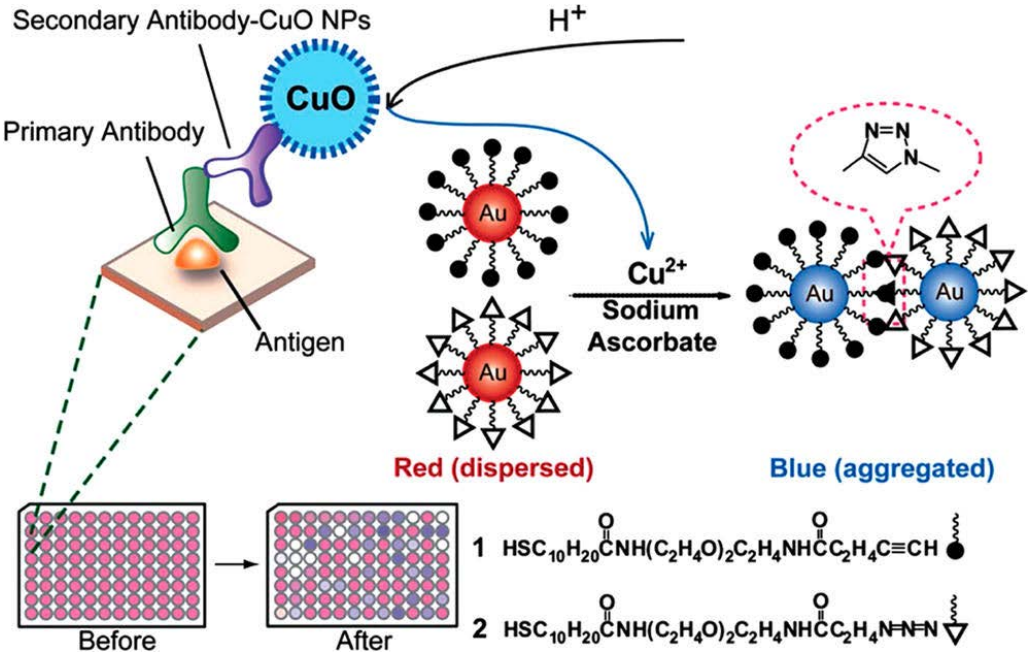


Figure 7. AuNPs-based immunoassay with the combination of CuO-mediated click chemistry. The CuO label was dissolved by acid to liberate copper ions, which act as a catalyst of click chemistry, and thus leading to the aggregation of the azide- and alkyne-functionalized AuNPss. The resulted color change from red to blue in turn reflected the existence of the target. Reprinted with Permission from ref 53. Copyright 2011 John Wiley and Sons

Figure 8

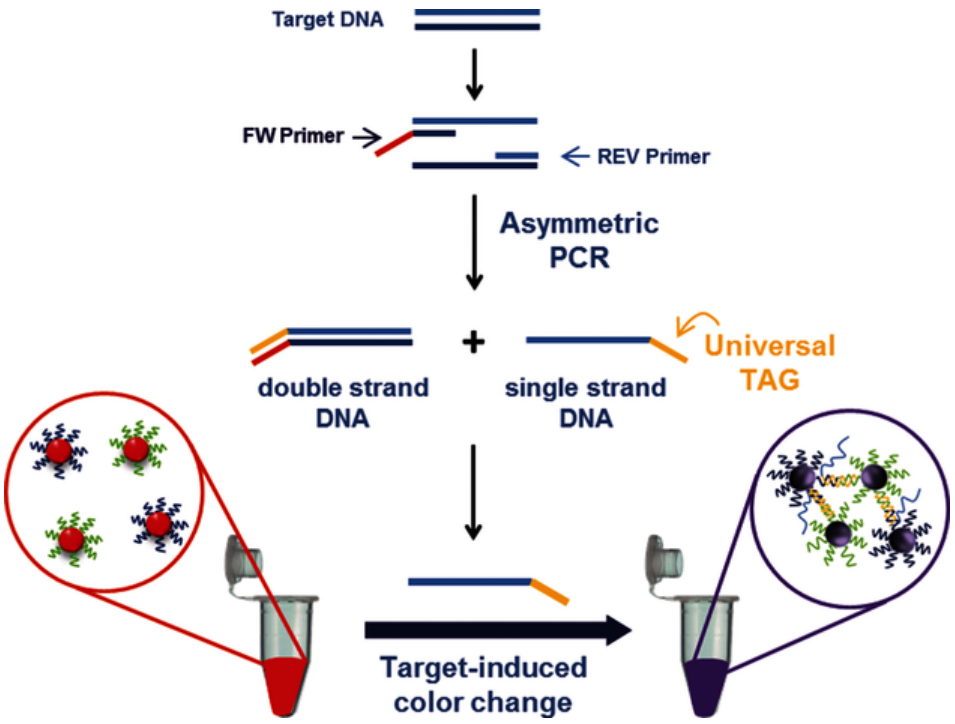


Figure 8 Assay principles. A standard reverse primer and a forward primer were used to to perform asymmetric PCR. After the amplification, single-stranded products depleted from the forward primer was accumulated. Upon addition of a sample containing the amplified target, two set of DNA probe-modified AuNPs would aggregate and color-shift because of the hybridization among the DNA probes and the universal tag. Reprinted with Permission from ref 37. Copyright 2016 John Wiley and Sons.

Figure 9

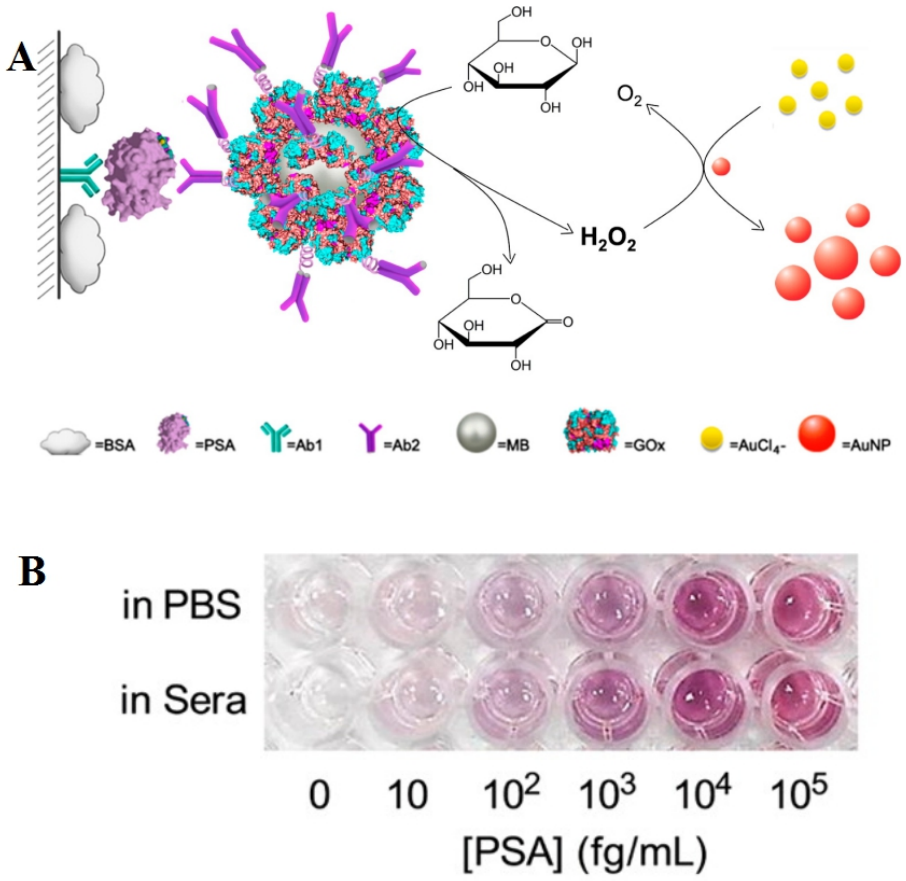


Figure 9 (A) Schematic illustration of the GOx-catalyzed growth of AuNPs-based immunoassay for the detection of prostate-specific antigen (PSA). PSA was first captured by antibody (Ab1) and then recognized by the GOx-conjugated detection antibody (Ab2) on the surfaces of MBs. The H_2O_2 generated from GOx-catalyzed oxidation of glucose could mediated the growth of the AuNPs, along with the solution changing to red from colorless. (B) The naked-eye detection of PSA in PBS and sera samples. Reprinted with Permission from ref 82. Copyright 2014 American Chemical Society.

Figure 10

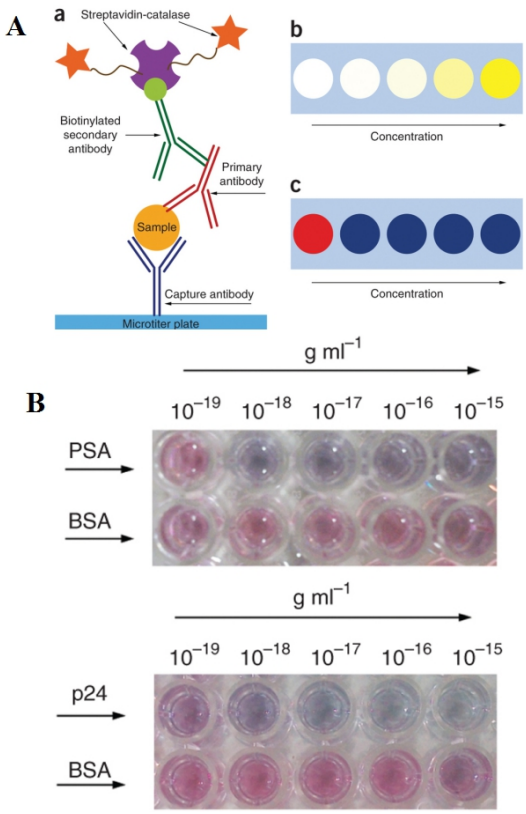


Figure 10 (A) Schematic diagram of ELISA (a) and expected results with conventional and plasmonic ELISA (b,c). Reprinted with Permission from ref 98. Copyright 2013 The Nature Publishing Group. (B) Visual detection using plasmonic ELISA for PSA and HIV-1 antigen p24. BSA-spiked samples were used as negative controls, which yield red-colored solutions, whereas target-containing samples yield blue-colored solutions. Reprinted with Permission from ref 95. Copyright 2012 The Nature Publishing Group.

Figure 11

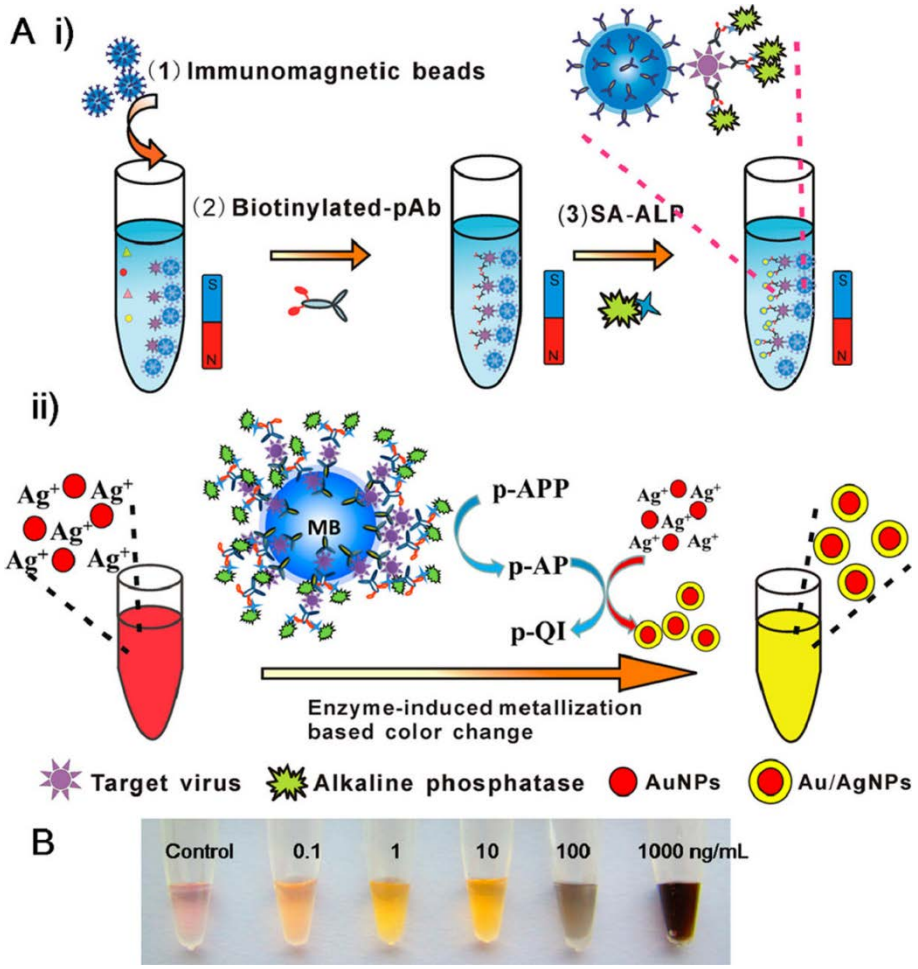


Figure 11 (A) Schematic illustration of the colorimetric immunoassay for H9N2 AIV. (i) immuno-reaction process using immnomagnetic beads (MB); (ii) signal-generation process based on enzyme-mediated silver reduction on AuNPs. (B) Visual detection of H9N2 AIV. Reprinted with Permission from ref 89. Copyright 2014 American Chemical Society.

Figure 12

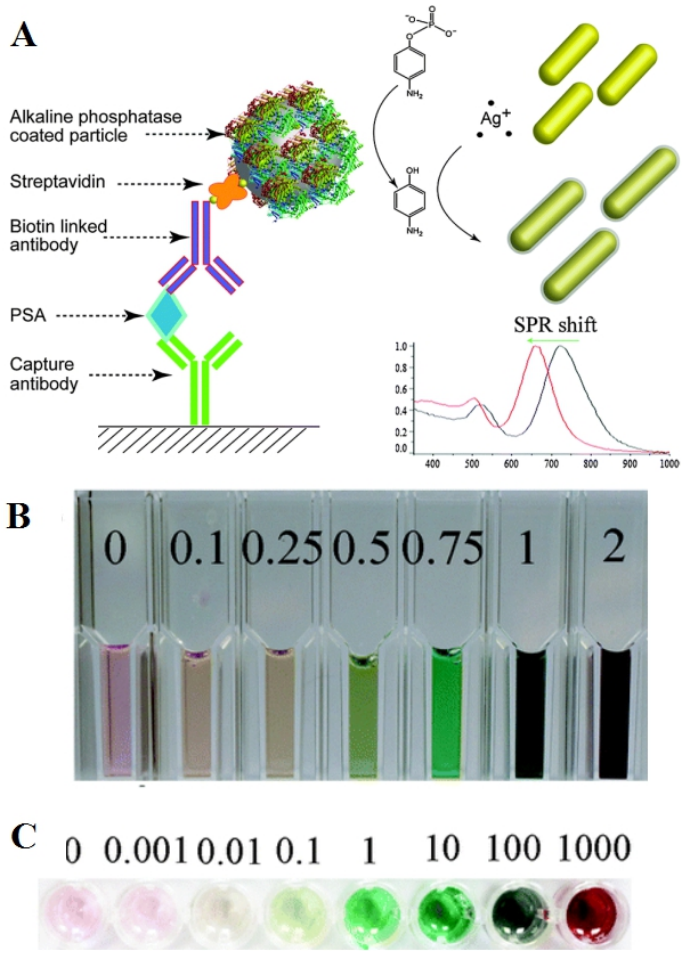


Figure 12 (A) Scheme of the colorimetric sensing principle for PSA. In the presence of PSA, alkaline phosphatase loaded on silica particles would be anchored to the substrate through sandwich immuno-reaction, which then catalyzed the producing of 4-aminophenol. The yielded 4-aminopheno could reduce silver ions to consequently deposit metallic silver on the AuNRs, resulting in the shift of LSPR peak of the AuNRs along with color-changed solution. (B) The color transition of the nanoparticle solution upon adding alkaline phosphatase with different concentrations; (C) The naked-eye detection of PSA with the concentrations range of 0~1000 pg mL^{-1} PSA. Reprinted with Permission from ref 93. Copyright 2015 The Royal Society of Chemistry

Figure 13

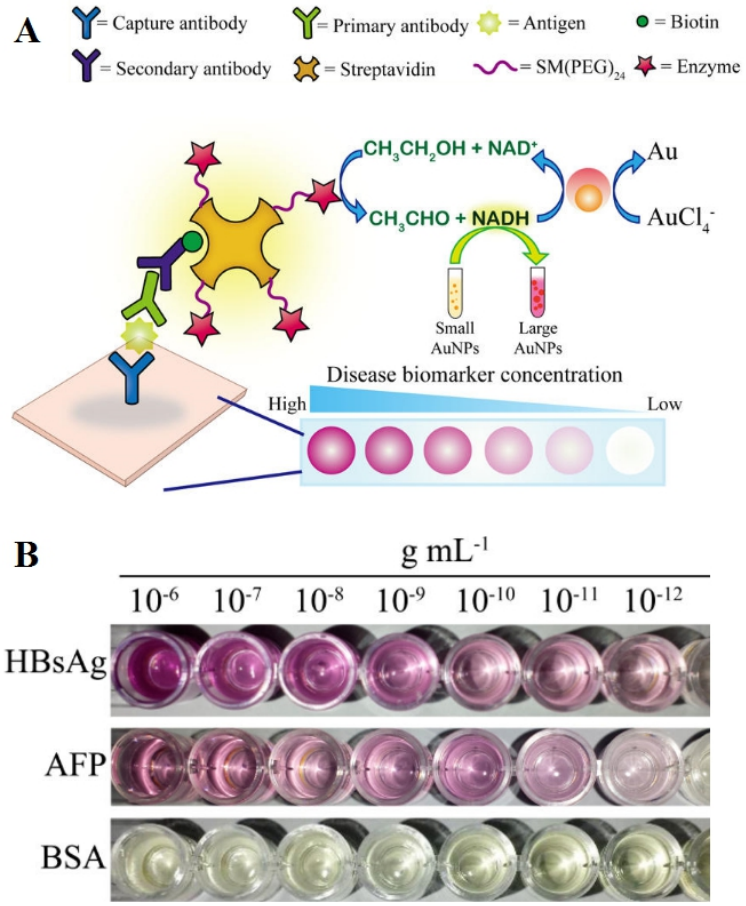


Figure 13 (A) Scheme of the enzymatic reaction-amplified ELISA.with plasmonic nanoparticles. (B) Colorimetric detection using plasmonic ELISA for the HBsAg, AFP, and BSA with the concentrations of 10^{-6} -10^{-13} g mL^{-1}, respectively**.** Reprinted with Permission from ref 88. Copyright 2015 American Chemical Society.

Figure 14

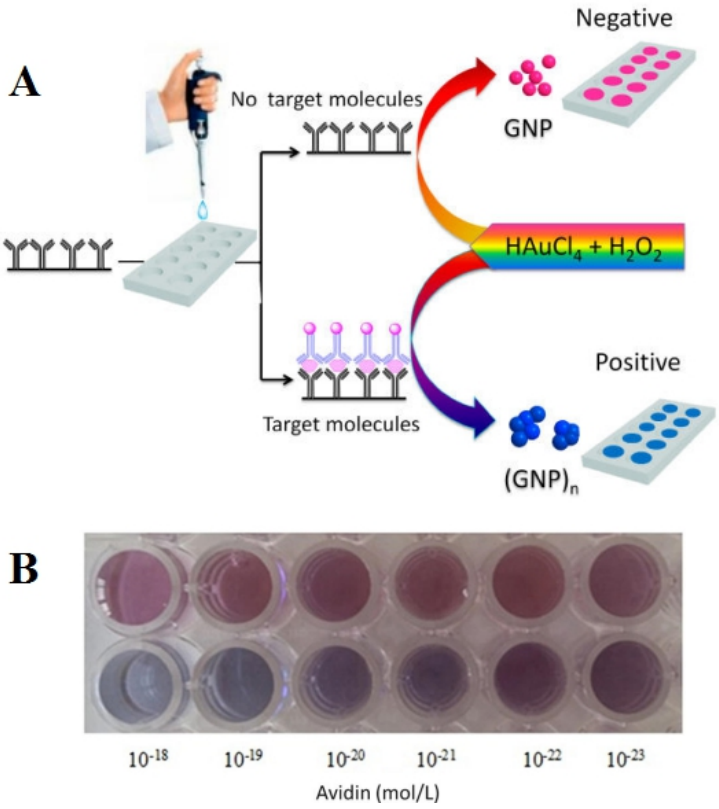


Figure 14. (A) Scheme of the sandwich plasmonic nanosenor and (B) colorimetric detection of avidin. Reprinted with Permission from ref 76. Copyright 2016 American Chemical Society.

Figure 15

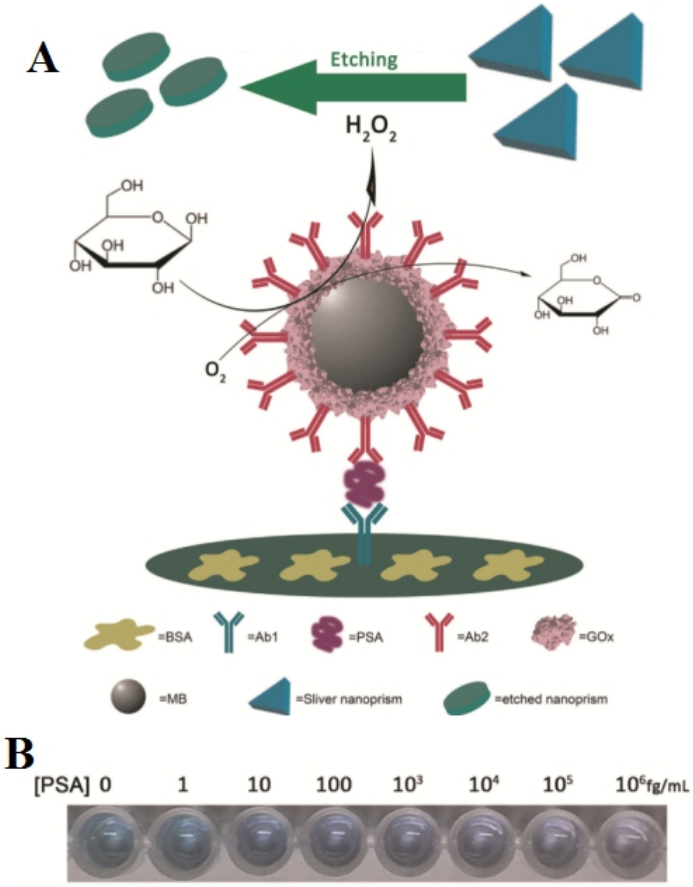


Figure 15 (A) Schematic illustration of the GOx-catalyzed etching of silver TNPs-integrated colorimetric immunosensor for the detection of PSA. (B) Colorimetric sensing of PSA with different concentrations in foetal bovine sera. Reprinted with permission from ref 109. Copyright 2015 Elsevier.

Figure 16

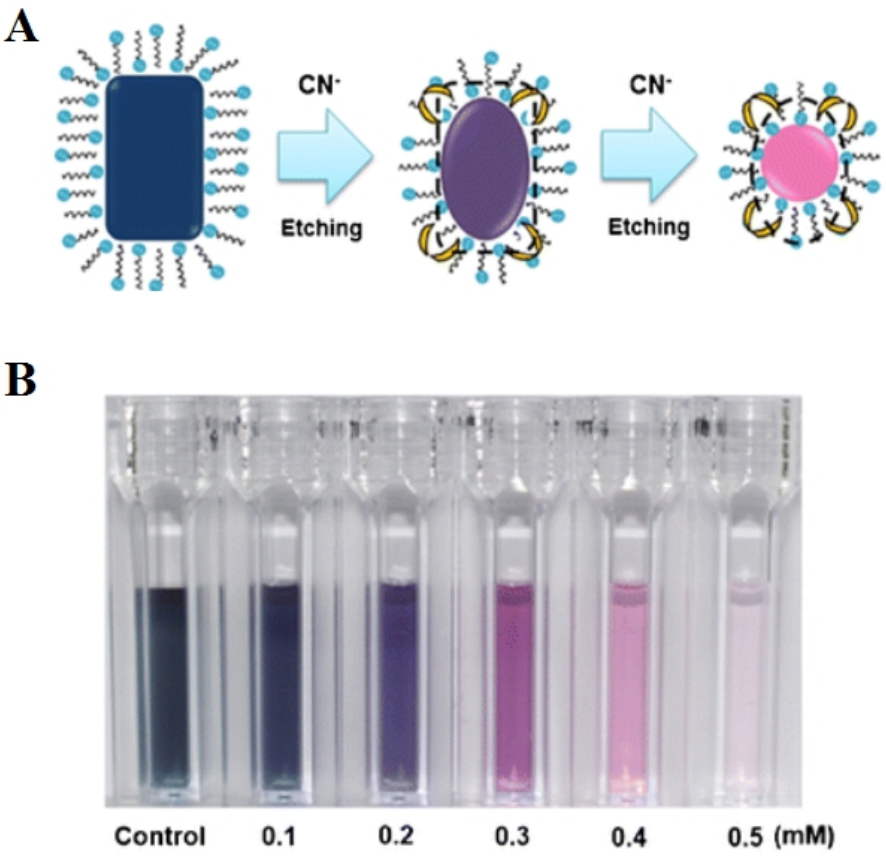
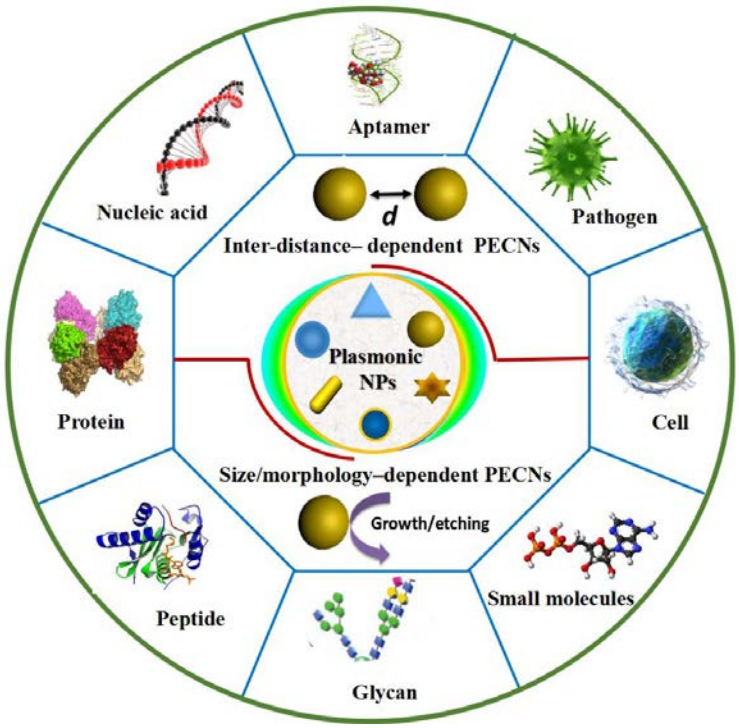


Figure 16 (A) Schematic illustration of the CN^--induced etching of AuNRs and (B) the color change of AuNRs solution by adding CN^- with different concentrations (0.1–0.5 mM). Reprinted with permission from ref 123. Copyright 2016 Springer.

For TOC only


Aptamer
Nucleic acid
Pathogen
d
Inter-distance– dependent PECNs
Plasmonic
NPs
Protein
Cell
Size/morphology–dependent PECNs
Growth/etching
Peptide
Small molecules
Glycan