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Gold nanocage-based lateral flow immunoassay for immunoglobulin G

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Abstract The authors describe a gold nanocage-based lateral flow strip biosensor (LFSB) for low-cost and sensitive detection of IgG. This protein was used as a model analyte to demonstrate the proof-of-concept. The method combines the unique optical properties of gold nanocages (GNCs) with highly efficient chromatographic separation. A sandwich-type of immunoreactions occurs on the GNC-based LFSB which has the attractive features of avoiding multiple incubation, separation, and washing steps. The captured GNCs on the purple test zone and control zone of the biosensor are producing characteristic purple bands, and this enables IgG even to be visually detected. Quantitatation was accomplished by reading the intensities of the bands with a portable strip reader. The LFSB fabrication and assay parameters were optimized. The biosensor displays a linear response in the 0.5 to 50 ng·mL^{-1} IgG concentration range, and it has a 15 min assay time. The detection limit is 0.1 ng·mL^{-1} of IgG, which is 2.5 times lower than that when using a gold nanoparticle-based LFSB. In our perception, this assay has a wide potential for the detection of other proteins and species for which respective antibodies are available.

Keywords Gold nanocages · Lateral flow strip · Immunoassay · Cellulose fiber · Nitrocellulose · Immunoglobulin G

Introduction

The detection and quantification of extremely low concentrations of proteins play pivotal roles in basic discovery research and clinical applications. Currently enzyme-linked immunosorbent assay (ELISA) is the gold standard method for protein analysis due to its sensitivity and accuracy. However ELISA still exists some drawbacks such as long analysis time, multiple incubation and washing steps. Automatic ELISA analyzers can overcome the above drawbacks; the cost of the instrument limits its wide applications, particularly in the low-resource settings. Lateral flow strip biosensors (LFSBs), also called immunochromatography strip test has gained increasing attention in protein analysis and clinical diagnosis because of its short assay time, easy-to-use, low cost and no requirements for skilled technicians. [1–3]. The LFSBs have been used for the visual detection of various targets such as protein [4, 5], chemical contaminants in food [6–10], single-nucleotide polymorphism [11], biological warfare agents [12] and nucleic acids [13]. One of the key components of LFSBs is the colored particles, which limits its sensitivity and reproducibility of the tests, Colored particles such as colloidal gold [14], colloidal selenium [15], colloidal carbon [16], Fe_3O_4 nanoparticle aggregates [17], latex [18], liposome [19], quantum dots [4, 20] etc., are used as tags to label the antibodies for visual detection of the analytes. In particular, colloidal gold or gold nanoparticles (GNPs) are the most commonly used particles for LFSBs due to their unique optical properties. Even though colloidal gold particle has relatively high absorption coefficient, the detection limit and sensitivity of GNP-based

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LFSBs remains to be improved and is usually the obstacle in real application. Numerous work has been carried out for sensitivity improvement of lateral flow strip methods [21, 22].

Gold nanocages (GNCs) have received considerable interest because of the inherent signaling mechanism. GNCs are new emerging gold nanomaterial which have shown outstanding properties in many fields [23–26]. Xia's group has prepared several noble metal nanocages, including GNCs, using a remarkably simple galvanic replacement reaction [27]. The UV visible absorbance spectra of GNCs demonstrated that peak position is tunable throughout the visible and into the near-infrared [28]. GNCs have 8 vertices which act as "hot spots"and are very sensitive to bulk and local dielectric changes. Due to sharp corners/edges, uniform size and perfect physicochemical properties, GNCs had been applied in colorimetric sensing and biomedical applications [29–31]. However, there are no reports on the application of GNCs in lateral flow immunoassay. Besides, Zhang has reported that GNCs can be produced by a one-pot method at room temperature without the use of gold seeds or any solid templates [32].

Inspired by these previous investigations, we first report the application of GNCs on the lateral flow biosensors and GNCs were used as colored particles for sensitive detection of protein. IgG was chosen as a model protein to demonstrate the proof-of-concept. The characteristics of the GNC-based LFSB were then compared to that of the GNP-based strip biosensor. The results indicated that GNC-based strip biosensors exhibited higher sensitivity. The other advantage of GNCs is that they are stable and not easy to aggregate during the conjugation process. We show here that GNCs are sensitive tag for the development of lateral flow strip biosensors for point-of-care or in-field detection of proteins. The promising properties of the GCN-based LFSB are reported in the following sections.

Experimental

Apparatus

The Portable strip reader, DT1030, was purchased from Shanghai Goldbio Tech. Co., LTD (Shanghai, China). The Biojet BJQ 3000 dispenser, Airjet AJQ 3000 dispenser, clamshell laminator and the guillotine cutting module CM 4000 were from Biodot LTD (Irvine, CA). A Hitachi HT7700 field transmission electron microscope (TEM; Tokyo, Japan) was used to characterize the gold nanocages.

Reagents and materials

Glass fibers (GFCP000800), cellulose fiber sample pads (CFSP001700), laminated cards (HF000MC100) and nitrocellulose membranes (HFB24004) were provided by Millipore (Bedford, MA). Polyvinylpyrrolidone (PVP K30) was obtained from Fluka (www.fluka.org). Na_3PO_4 $12H_2O$, $HAuCl_4$, trisodium citrate, sucrose, Tween 20, Triton X-100, phosphate buffer saline (PBS, pH 7.4, 0.01 mol L^{-1} NaH_2PO_4 and Na_2HPO_4 containing 0.9% NaCl), silver nitrate ($AgNO_3$), hexamethylenetetramine (HTM, $C_6H_{12}N_4$), ascorbic acid, bovine serum albumin (BSA), human serum albumin (HSA) and casein (from bovine milk) were purchased from Sigma-Aldrich (www.sigmaaldrich.com). Rabbit IgG, Polyclonal goat anti-rabbit immunoglobulin G (IgG) antibody, mouse anti goat immunoglobulin G secondary antibody and human IgM were purchased from Thermo Scientific (www.thermofisher.com).

Preparation of gold nanocages (GNCs)

GNCs were synthesized according to Zhang's report [32]. Briefly,3.0 mL of 0.75 mmol L^{-1} $HAuCl_4$ solution was added to 3.0 mL of 0.03 mol L^{-1} HMT solution. The color of the $HAuCl_4$ solution changed from light yellow to clear. Then, 3.0 mL of 0.30 mom L^{-1} PVP and 100 μL of 0.01 mol L^{-1} $AgNO_3$ were added to the solution. After gently stirred, 50 μL of 0.08 mol L^{-1} ascorbic acid was added. The solution was stirred for another 10 s to ensure complete mixing. Then, it was allowed to react without agitation for 12 h at room temperature. The resulting GNCs solution (48.43 μg mL^{-1}) was centrifuged and washed with ethanol and water for several times and then dropped onto the substrates for characterizations. The resulting GNCs solution was stored in dark bottles at 4 °C and used to prepare the GNC/antibody conjugate.

Preparation of gold nanoparticles (GNPs)

GNPs with average diameter 15 ± 3.5 nm were prepared according to the reported methods with slight modifications [33]. All glassware used in this preparation was thoroughly cleaned in aqua regia (three parts HCl and one part HNO_3), rinsed in doubly distilled water, and oven-dried prior to use. In a 500 mL, round-bottom flask, 100 mL of 0.01% $HAuCl_4$ in doubly distilled water were brought to boil with vigorous stirring, followed by the addition of 4.5 mL of 1% trisodium citrate. The solution turned deep purple within 20 s, and the final color changed to wine-red after 60 s. Boiling was pursued for an additional 10 min; the heating source was removed, and the colloid solution was stirred for another 15 min. The resulting GNPs solution (55.5 μg mL^{-1}) was stored in dark bottles at 4 °C and used to prepare the GNP/antibody conjugate.

Preparation of GNC/antibody conjugate.

GNC/antibody conjugates were prepared according to the reported protocol with modification [34]. Briefly, 10 μL of the goat anti-rabbit IgG antibody was added into 0.25 mL of the

5-fold concentrated GNCs solution (pH 9.0) followed by incubation for 2 h at room temperature with gentle shaking. Then, 25 μL of BSA (10%) was added into the solution and reacted for 30 min to block the unoccupied surface on GNCs. After centrifuged at 15000 rpm for 10 min, the supernatant was discarded and the pallet was rinsed by 0.01 mol L^{-1} PBS for two times and resuspended in 1 mL of eluent buffer (an aqueous solution containing 20 mmol L^{-1} Na_3PO_4, 5% BSA, 0.25% Tween 20, and 10% sucrose) to increase the stability of GNC-labeled antibody and to minimize non-specific adsorption during the assays.

Preparation of GNP/antibody conjugate.

For comparison experiment,GNP/antibody conjugates were prepared according to the reported protocol [5, 35]. 0.01 mg of Ab 1 was added to 1.0 mL of five fold-concentrated GNPs (pH 9.0). The mixture was gently incubated for 1 h and blocked by 0.1 mL of 10 wt% BSA for 30 min. The obtained solution was centrifuged at 12,000 rpm for 18 min, and the nanoparticles were washed with PBS (1% BSA) 3 times. The resulting ruby sediments were dispensed in 1.0 mL of buffer containing 20 mM $Na_3PO_4 \cdot 12H_2O$, 0.25% Tween 20, 10% sucrose, and 5% BSA.

Preparation of the lateral flow strip biosensor (LFSB)

The sample application pad (17 mm × 30 cm) was made from cellulose fiber (CFSP001700, Millipore) and was soaked with a buffer (pH 8.0) containing 0.25% Triton X-100, 0.05 M Tris–HCl, and 0.15 mmol L^{-1} NaCl. Then the pad was dried at room temperature and stored in desiccators at 4 °C. Test and control zones on the nitrocellulose membrane (25 mm × 30 cm) were prepared by dispensing polyclonal goat anti-R-IgG antibody (test zone, 1.2 mg mL^{-1}) and mouse anti goat IgG secondary antibody (control zone, 200 μg mL^{-1}) solutions, respectively. The distance between test and control zone was 3 mm. The membrane was dried at room temperature for 1 h and stored at 4 °C. Finally, all of the parts were assembled on a plastic adhesive backing layer (typically an inert plastic, e.g., polyester) using the Clamshell Laminator. Each part overlapped 2 mm to ensure the solution migrating through the strip during the assay. Strip with a 3 mm width were cut by using the Guillotin cutting module CM 4000 cut module.

Sample assay procedure

Before test, 7 μL of GNC/antibody conjugate was spotted on the conjugate pad and dried for 5 min. In a typical experiment, 100 μL of sample solution containing a desired concentration of IgG in PBST buffer (0.01 mol L^{-1} PBS with 0.05% Tween 20) was applied to the sample application zone. After 10 min, another 50 μL of PBST buffer was added to wash the strip. The bands were visualized within 15 min. For quantitative measurements, the strip was inserted into the strip reader DT1030, in which the optical intensities of the test line and control line can be recorded simultaneously by using the "GoldBio strip reader" software.

For comparison experiment**,** GNP-based LFSB was used to detect IgG under the optimized experimental conditions [5, 35]. Four microliter of GNP/antibody conjugate was spotted on the conjugate pad and dried for 5 min. In a typical experiment, 100 μL of sample solution containing a desired concentration of IgG in PBST buffer (0.01 mol L^{-1} PBS with 0.05% Tween 20) was applied to the sample application zone. After 10 min, another 50 μL of PBST buffer was added to wash the strip. The bands were visualized within 15 min.

Results and discussion

Principle of GNC-based LFSB

The morphology of the GNCs was investigated by transmission electron microscopy (TEM). Fig. 1 demonstrates that the GNCs possess hollow square nanostructures and have an average diameter of 50 nm (n = 50). The GNCs were then used as tag to label the anti-IgG (antibody), and the resulting GNC-anti-IgG conjugate was dispensed on the conjugate pad of LFSB to detect IgG. Figure 2 illustrates the principle of the GNC-based LFSB for the detection of IgG. Goat anti-rabbit IgG antibody and mouse anti-goat IgG antibody were pre-immobilized on the nitrocellulose membrane to form the test zone and control zone, respectively. GNC/anti-IgG conjugate was dispensed on the conjugate pad (glass fiber). The sample solution containing rabbit IgG is applied on the sample application pad. The solution migrates by capillary action and passes the conjugate pad, and then rehydrates the GNC/anti-IgG conjugates. The immune- complex (GNC/anti-IgG-IgG) is formed between the rabbit IgG and anti-rabbit IgG of the GNC/ anti-IgG conjugates, and continues to migrate along the strip. The complex is captured on the test zone through the second immunoreaction between rabbit IgG and the immobilized anti-rabbit IgG. The accumulation of GNCs in the test zone of the nitrocellulose membrane is visualized as a characteristic purple band. The excess of GNC/ anti-IgG conjugates continue to migrate and are captured on the control zone by the immuno events between goat anti-rabbit IgG and mouse anti-goat antibody, thus forming a second purple band (Fig. 2 a). In the absence of target IgG, no purple band is observed in the test zone. In this case, a purple band (control line) shows that the LFSB works well (Fig. 2b). Qualitative analysis is simply performed by observing the color change of the test zone, and quantitative analysis is realized by reading the optical intensity of the test line with the portable strip reader (Fig. 2c).

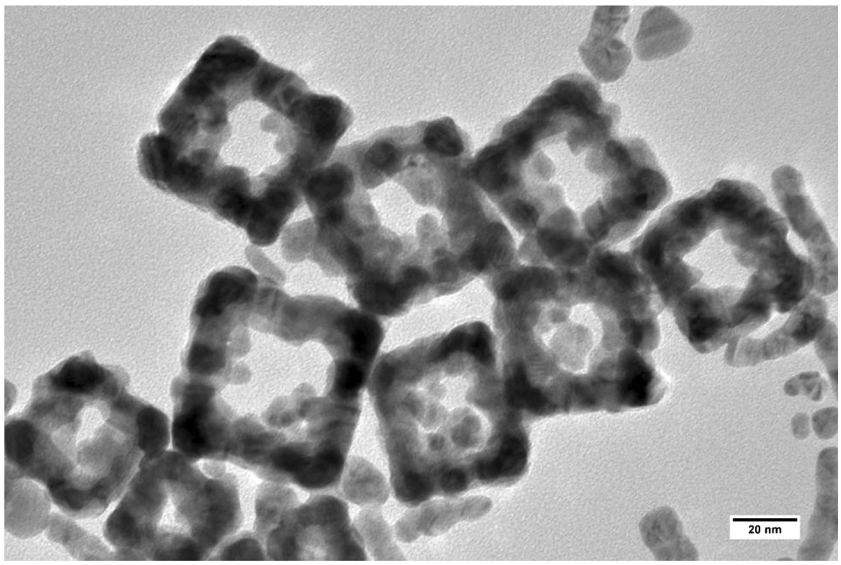

Fig. 1 TEM image of gold nanocages

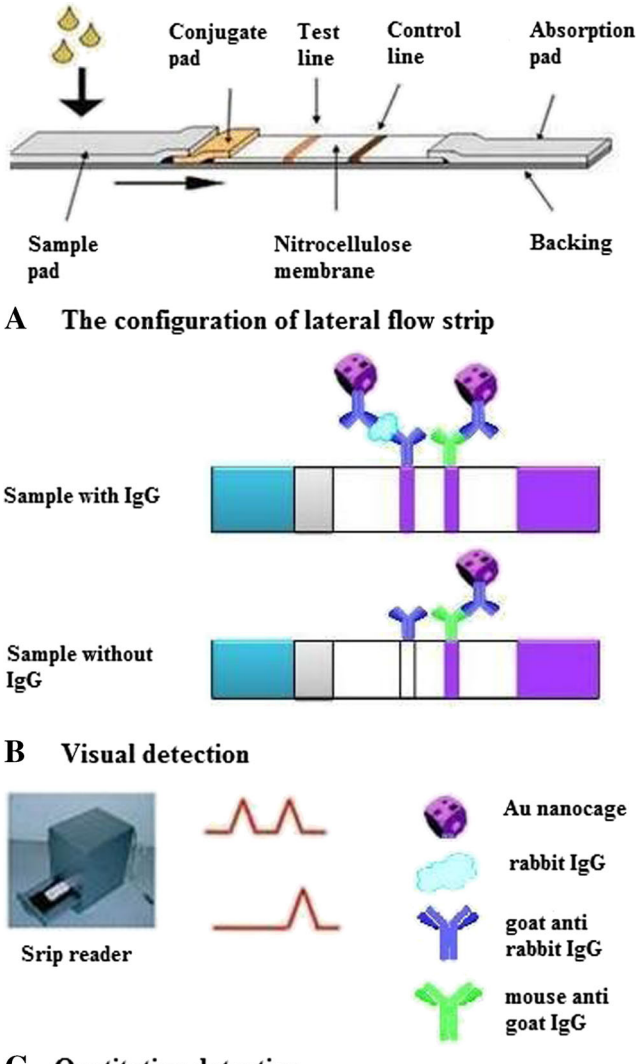

Fig. 2 Schematic of the configuration and measurement principle of the GNC-based LFSB: **a** configuration of the biosensor; **b** visual detection; **c** quantitative detection with a portable strip reader

Figure 3 displays the typical responses of 0 ng mL^{-1} (a), 0.5 ng mL^{-1} (b), 5 ng mL^{-1} (c), 50 ng mL^{-1} (d) of IgG on the LFSB. The intensities of the bands were recorded by the strip reader. Well-defined peaks are observed, and the peak areas are proportional to the amount of captured GNCs in the test zone (left side) and control zone (right side). With the increase of the concentration of IgG, the peak areas of test zone raised.

Optimization of experimental parameters.

The following parameters were optimized: (a) Effect of IgG antibody amount on the test zone; (b) Effect of amount of GNC/ anti-IgG conjugates; (c) Effect of anti-IgG amount added for GNCs modification; (d) Effect of types of nitrocellulose membrane; (e) effect of running buffer. Respective data and Figures are given in the Electronic Supporting Material. We found the

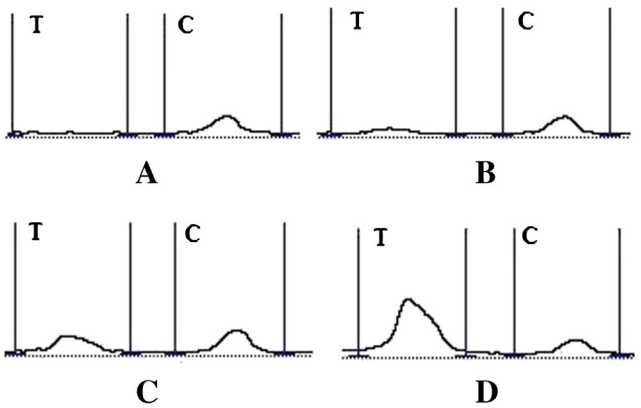

Fig. 3 Typical recorded responses of LFSBs with a portable strip reader after applying the sample solutions (right: optical response of the control line; left: optical response of the test line). 0 ng mL^{-1} (**a**), 0.5 ng mL^{-1} (**b**), 5 ng mL^{-1} (**c**), 50 ng mL^{-1} (**d**) of IgG. Assay time: 15 min; all sample solution were prepared with PBST buffer

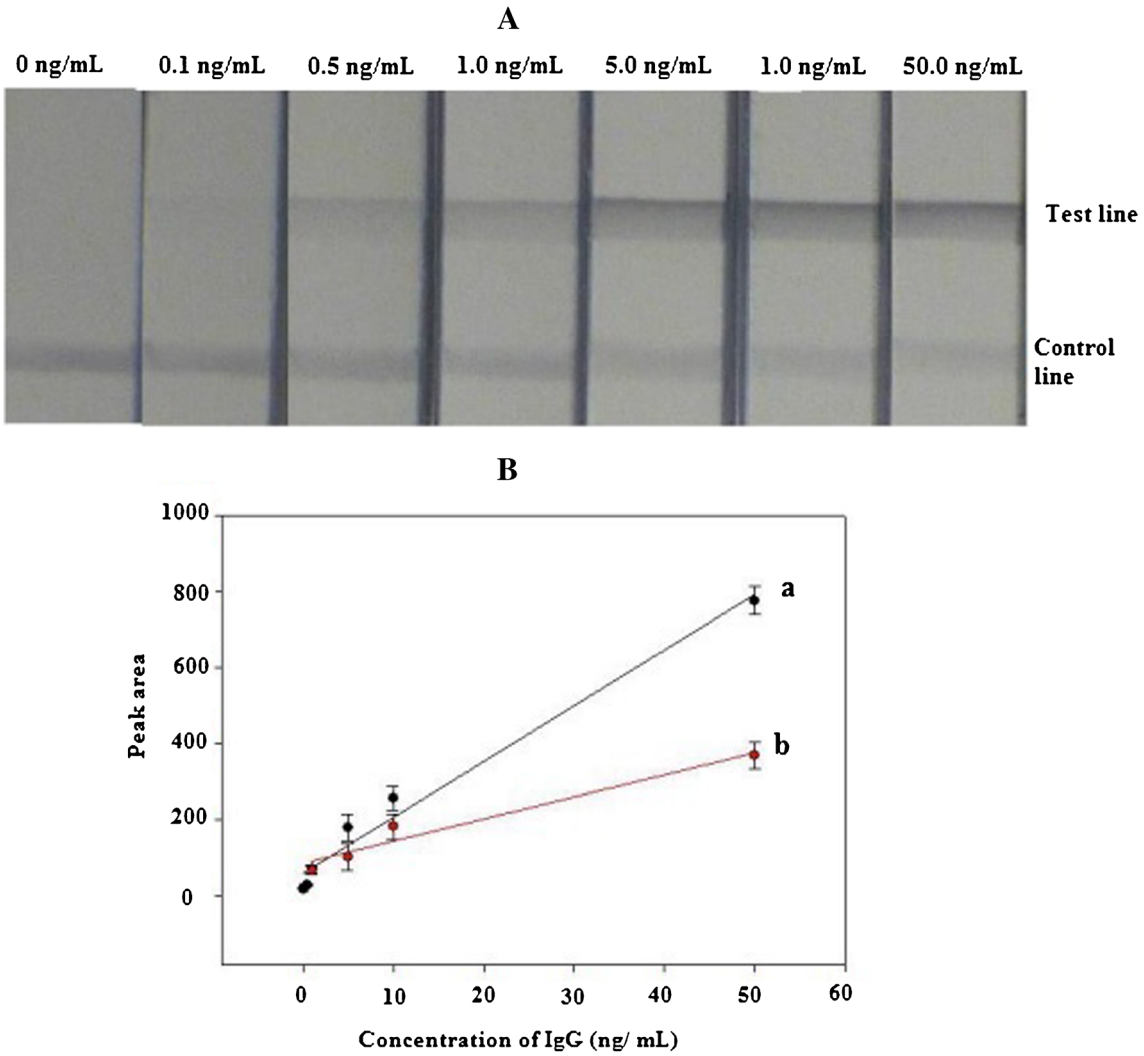

Fig. 4 **a** Photo images of LFSB in the presence of different concentrations of IgG. **b** The calibration curve of LFSB based on gold nanocages (**a**) and gold nanoparticles (**b**), respectively

following experimental conditions to give best results: (a) dispensing test zone two times; (b) loading 7 μL of GNC/anti-IgG conjugates on conjugate pads; (c) using 46 μg mL^{-1} of anti-IgG to prepare the GNC/anti-IgG conjugates; (d) using HFB 18004 to prepare the LFSB; (e) using PBST buffer as running buffer.

Table 1 An overview on recently reported nanomaterial-based methods for determination of immunoglobulin G

Material/method used	Dynamic range	Detection limit (ng mL^{-1})	References
Gold-Nanoparticle-Decorated Silica Nanorod -based LFSB	0.05 − 2 ng mL^{-1}	0.01	[35]
surface plasmon resonance biosensor by Ag nanocubes/chitosan composite	0.600–40.00 μg mL^{-1}		[36]
Naked-eye ELISA-like assay	0.7–100 ng mL^{-1}	0.3	[37]
SERS immunoassay based on gold nanoparticles		1.9	[38]
Lab-in-a-syringe using gold nanoparticles		1.0	39]
chemiluminescence immunodevice	0.1–10.0 ng/mL	0.03	[40]
Au nanocage-based LFSB	0.5-50 ng mL^{-1}	0.1	This work

Analytical performances.

Under optimal experimental conditions, the performance of the GNC-based LFSB was examined with different concentrations of target IgG. Quantitative detections were performed by recording the intensities of the test lines with the portable strip reader. Well-defined peaks were observed, and the peak areas increased with the increase of IgG concentration. Figure 4a presents the typical photo images of the LFSB in the presence of different IgG concentrations. The resulting calibration plot of the peak areas versus target IgG concentration is linear in the range of 0.5 to 50 ng mL^{-1} with the detection limit of 0.1 ng mL^{-1} at 3σ (Fig. 4 b, curve a). Table 1 displays an overview on recently reported nanomaterial-based methods and this work for determination of immunoglobulin G. From Table 1, it can be see that the detection limit of this work is lower than that of some reported methods. Although Xu's report [35] and Li's method [40] have better detection limit, the linear range of Xu's report is narrower than that of this work, and chemiluminescence immunodevice needs expansive instrument. The reproducibility of the LFSB was studied. Samples with concentration of 5 ng mL^{-1} IgG were loaded on six different LFSBs that gave reproducible signals with a relative standard deviation (RSD) of 5.3%.

To compare the analytical performances of the GNC-based LFSB with that of traditional GNP-based LFSB, GNP/anti-IgG conjugate was also used to prepare the LFSB for the determination of IgG. Figure 4b, curve b shows the calibration curves of GNP-based LFSB. The linear equations, detection limits, and sensitivities of the two types of biosensors are summarized in Table 2. One can see that the sensitivity of GNC-based LFSB is 2.5 times higher than that of GNP-based strip biosensor.

The specificity of the GNC-based on LFSB

A series of probable interferences were used to investigate the selectivity of the biosensor. Figure 5 presents the response histograms of GNC-based LFSB in the presence of an excess of nonspecific proteins (HSA, IgG, IgM, and casein), which are present in high concentrations in a biological matrix. As shown in Fig. 5, a high response is observed when 5 ng mL^{-1} IgG was tested, whereas the negligible signals are obtained from other proteins, indicating the excellent specificity of the LFSB.

Table 2 Comparison of analytical performance of LFSBs based on GNCs and GNPs

Strip	Dynamic range ngng mL^{-1}	Detection limit ngng mL^{-1}	Linear equation	Sensitivity (slope)
GNCs based	0.5–50	0.1	Y = 58.91 + 14.62C	14.62
GNPs based	1–50	0.5	Y = 84.53 + 5.82C	5.82

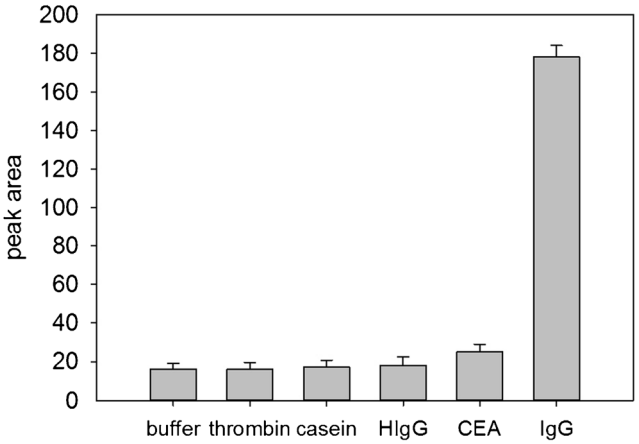

Fig. 5 The specificity of the LFSB

Conclusion

In summary, we have demonstrated that the gold nanocages can be used as sensitive tag to develop LFSB for quantitative detection of IgG. Owing to the significant optical prefect, the gold nanocages offer improved visual detection sensitivity in detecting IgG and the sensitivity of gold nanocage-based lateral flow strip biosensor is 2.5 times higher than that of gold nanoparticle-based lateral flow strip biosensor. The current investigations thereby provide an alternative strategy for developing sensitive LFSB through gold nanocages.

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Compliance with ethical standards The author(s) declare that they have no competing interests.

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