



# Replacement of cetyltrimethylammoniumbromide bilayer on gold nanorod by alkanethiol crosslinker for enhanced plasmon resonance sensitivity

Justin Casas, Meenakshi Venkataramasubramani, Yanyan Wang, Liang Tang\*

Department of Biomedical Engineering, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249, USA

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## ABSTRACT

Surface modification of gold nanorods (GNRs) is often problematic due to tightly packed cetyltrimethylammoniumbromide (CTAB) bilayer. Herein, we performed a double phase transfer ligand exchange to achieve displacement of CTAB on nanorods. During the removal, 11-mercaptoundecanoic acid (MUDA) crosslinker is simultaneously assembled on nanorod surfaces to prevent aggregation. The resulting MUDA-GNRs retain the shape and position of plasmon peaks similar to CTAB-capped GNRs. The introduction of carboxyl groups allows covalent conjugation of biological receptors in a facile fashion to construct a robust, label-free biosensor based on localized surface plasmon resonance (LSPR) transduction of biomolecular interaction. More importantly, smaller MUDA layer on the GNRs reduces the distance of target binding to the plasmonic nanostructure interface, leading to a significant enhancement in LSPR assay sensitivity and specificity. Compared to modification using conventional electropolymer adsorption, MUDA-coated gold nanosensor exhibits five times lower detection limit for cardiac troponin I assay with a high selectivity.

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## 1. Introduction

In sensor applications, the optical transduction by gold nanoparticles is based upon the phenomenon of localized surface plasmon resonance, i.e. LSPR (Lee and El-Sayed, 2006). According to the plasmon hybridization mode (Prodan et al., 2003), the plasmon resonance frequency is largely determined by the geometry of the colloidal metal structure, as a result of electrostatic interactions between confined electrons distributed over the surfaces of the metal conductor. LSPR offers the advantage of the direct label-free detection method that relies on the measurement of refractive index changes accompanied with the binding of target analyte. Gold nanostructures including shell, ring, prism, star, cage and rod have been fabricated to exploit the full potential of the geometry dependent LSPR for a variety of applications from photonics to biological investigations (Aizpurua et al., 2003; Prodan and Nordlander, 2004; Radloff et al., 2005; Wang and Halas, 2006; Wang et al., 2012). From the viewpoint of plasmon sensitivity and tunability, gold nanorod (GNR) has been at the center of attention (Chen et al., 2013; Kim et al., 2012).

There are several methods which have been widely reported for the GNR fabrication, such as the seed-mediated growth

method (Jana et al., 2001; Nikoobakht and El-Sayed, 2003), electrochemical synthesis (Yu et al., 1997), and nano-lithography (Billot et al., 2006). Among these, seed mediated growth is the most common strategy because of simplicity and availability of LSPR wavelength from visible to infrared red region. Although cetyltrimethylammoniumbromide (CTAB) is an essential capping agent to prevent particle aggregation with improved solubility, the resulting bilayer tightly packed onto the nanorod surface usually blocks access for surface modification with bioconjugates. CTAB prefers to bind with the longitudinal side surface of the nanorod rather than the end surface (Gao et al., 2003). Spontaneous reaction of thiolated molecules with GNRs only occurs at the two end faces for partial activation. These factors are problematic owing to nonspecific adsorption, cytotoxicity, and instability. The drawbacks have impaired the use of CTAB-capped nanorods in biological applications, especially compared to nanospheres. As such, it is imperative to find effective methods for the surface modification of GNRs.

To date, a variety of methods have been investigated to improve GNR surface modification (Huang et al., 2013; Liao and Hafner, 2005; Mitamura et al., 2009; Wijaya and Hamad-Schifferli, 2008; Yu et al., 2007). For example, additional layer(s) of silica or polyelectrolyte coating via physical adsorption was used to passivate the CTAB bilayer to allow their functionalization for specific applications (Gole and Murphy, 2005; Sendroui et al., 2009). However, there is a negative effect on LSPR sensitivity as additional

\* Corresponding author. Tel.: +1 210 458 6557; fax: +1 210 458 7007.

E-mail addresses: [liang.tang@utsa.edu](mailto:liang.tang@utsa.edu), [fancy5857@gmail.com](mailto:fancy5857@gmail.com) (L. Tang).

coatings will increase the distance between the GNR surface and target molecules (Tian et al., 2012). As such, effective removal of CTAB bilayer is desirable for sensing purposes. Due to the high binding affinity to gold, alkanethiols such as 11-mercaptoundecanoic acid (MUDA) are normally used to replace CTAB molecules (Cao et al., 2012; Yu et al., 2007). Compared to other alkanethiols, MUDA is smaller and its carboxyl terminals can be further functionalized to conjugate with biological receptors. Although shorter chain thiolated carboxylic agents such as cysteamine are more favorable to bring binding event closer to the nanorod surface, they tend to cause nanoparticle aggregation due to instability. Additionally, most of the current work is focused on the improvement in efficient surface modification of CTAB-capped GNRs. There is a lack of elucidation of how these biofunctionalization improvements can affect the biosensing performance in pursuit of low sensitivity and high specificity. These study would be highly meaningful and desirable to improve clinical diagnosis by biomarker detection.

In this paper, we explore a facile process of MUDA displacement of CTAB molecules bound on nanorod surface by double phase transfer ligand exchange. Further immobilization of antibody onto the fully activated MUDA-coated GNR surfaces was achieved with robust covalent bindings. More importantly, the effect of the MUDA modified GNRs on distance-dependent LSPR sensitivity was studied as compared to electrostatic adsorption of polymeric coating over CTAB–GNRs. We attribute the sensing performance enhancement to fully activated nanorods using ligand exchange to remove CTAB bilayer, leading to a dramatically decreased sensing distance from the LSPR surface. To demonstrate the practical application of the functional GNR biosensor with MUDA crosslinker, we performed a model study for human cTnI quantification, whose level is indicative of myocardial infarction in clinical diagnostics (Venge et al., 2009). The sensing performance in terms of sensitivity and specificity was systematically evaluated.

## 2. Materials and methods

### 2.1. Materials

Hydrogen tetrachloroaurate trihydrate ( $\text{HAuCl}_4$ ; 99%), sodium borohydride ( $\text{NaBH}_4$ ; 99%), cetyltrimethylammoniumbromide (CTAB), L-ascorbic acid (AA), silver nitrate ( $\text{AgNO}_3$ ; 99%), dodecanthiol (DDT), 11-mercaptoundecanoic acid (MUDA; > 95%), N-hydroxysulfosuccinimide (Sulfo-NHS), 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimidehydrochloride (EDC), regular human plasma, fibrinogen, bovine serum albumin and poly(sodium-p-styrenesulfonate) (PSS; MW: 70,000) were obtained from Sigma-Aldrich (St. Louis, MO). Highly purified human cardiac troponin I (cTnI) and specific murine monoclonal antibody were from Fitzgerald Industries (Acton, MA).

### 2.2. Fabrication and characterization of Au nanorods

Gold nanorods were chemically synthesized using seed mediated growth method as described previously with modifications (Sau and Murphy, 2004). Typically, a seed solution of gold nanospheres (5–10 nm) was prepared by mixing gold chloride (5 mL, 0.5 mM) with 5 mL (0.2 M) CTAB for 1 min and adding 0.6 mL (10 mM) fresh, ice cold sodium borohydride under vigorous stirring. After 2 min of mixing, the solution was incubated in water bath at 25–27 °C for at least 2 h. The seed solutions were then added to growth media ( $\text{HAuCl}_4$ , 1 mM; CTAB, 0.2 M;  $\text{AgNO}_3$ , 4 mM; and AA, 78.8 mM) and incubated at 27 °C overnight to allow complete rod growth.

Absorption spectra of the synthesized GNRs were collected with a UV–vis spectrophotometer (Beckman Colter). Electron

microscopy images of the nanorods were taken using Hitachi scanning electron microscope (SEM) and elemental analysis was carried out on a Joel SEM equipped with X-ray energy dispersive analysis (EDAX). For each sample, the size of 200 particles was measured to obtain the average nanoparticle dimension, aspect ratio, and yield.

### 2.3. Surface modification and biofunctionalization of Au nanorods

To construct a specific nanorod probe for biological detection, surface modification is required to functionalize with biological receptors such as antibody. Herein, we investigated two methods as the following.

#### 2.3.1. Double phase transfer ligand exchange

Seed mediated growth method results in the nanorod surfaces covered by a CTAB bilayer. A phase transfer ligand exchange using DDT and subsequently MUDA as reported earlier with modifications were performed to efficiently replace CTAB molecules bound on the Au surfaces (Wijaya and Hamad-Schifferli, 2008). Briefly, 4 mL dodecanthiol and 8 mL acetone were sequentially added to 2 mL highly concentrated nanorod solution and gently swirled. A clear separation of the aqueous and organic layers was present with the DDT coated gold nanorods in the top organic layer. After separation, 2 mL toluene and 9 mL methanol were added to the top layer. The solution was then centrifuged (5000 rpm for 15 min) into a pellet and resuspended in 2 mL toluene via sonication (20 min). This suspension was then added under vigorous stirring to 9 mL MUDA (0.01 M in toluene) at 70 °C. After 15 min the solution was allowed to cool down to room temperature as the nanoparticles settled to the bottom. The toluene solution was decanted and the rods were resuspended in 3 mL toluene and allowed to settle, followed by a second wash with 3 mL isopropyl alcohol to deprotonate the MUDA. The resulting MUDA become negatively charged at physiological pH, thereby minimizing electrical repulsion to little nonspecific binding. The aggregates are finally redispersed in 1 mL of Tris-borate EDTA buffer. After the CTAB was replaced by the MUDA, the carboxylic groups ( $-\text{COOH}$ ) at the nanorods surface were activated by EDC/sulfo-NHS (2:1 mg/mL) to form a stable NHS ester. The NHS ester-activated crosslinker then reacted with the amine groups to yield  $\text{NH}-\text{CO}$  bonds to covalently immobilize anti-cTnI molecules on the surfaces of GNRs.

#### 2.3.2. Electrostatic coating method

Physical adsorption of negatively charged PSS polymers to wrap over positively charged CTAB bilayer on the nanorod surfaces was achieved by mixing GNRs with PSS solution (0.5–20 mg/mL) in the presence of 1 mM NaCl. After vigorous stirring, the solution was incubated at room temperature for 1 h. Afterwards, the solution was centrifuged at 8500 rpm for 12 min to remove excessive PSS molecules. The PSS-coated nanorods were then redispersed in 10 mL of PBS buffer, followed by addition of 5 mL of monoclonal antibody against cardiac troponin I (50  $\mu\text{g/mL}$ ) with sonication for 1 h.

### 2.4. Label free LSPR assay based on gold nanorod probes

Once the specific antibody is immobilized on the rod surface, the absorption spectrum of the functional GNR sensor was taken as a baseline reading. To carry out the immuno-reaction and the resulting spectral shift measurement, biological samples spiked with various cTnI concentrations (0.5–1 mL) were incubated with equal volume of functional GNR probes prepared by ligand exchange and PSS coating, respectively, for 1 h under mild

agitation (500 rpm shaker). The absorption spectra were then measured using UV–vis spectroscopy to observe a pronounced red shift of the longitudinal plasmon band of gold nanorods upon target binding. The magnitude of the peak wavelength shift is highly sensitive to the amount of cTnI in samples.

### 3. Results and discussion

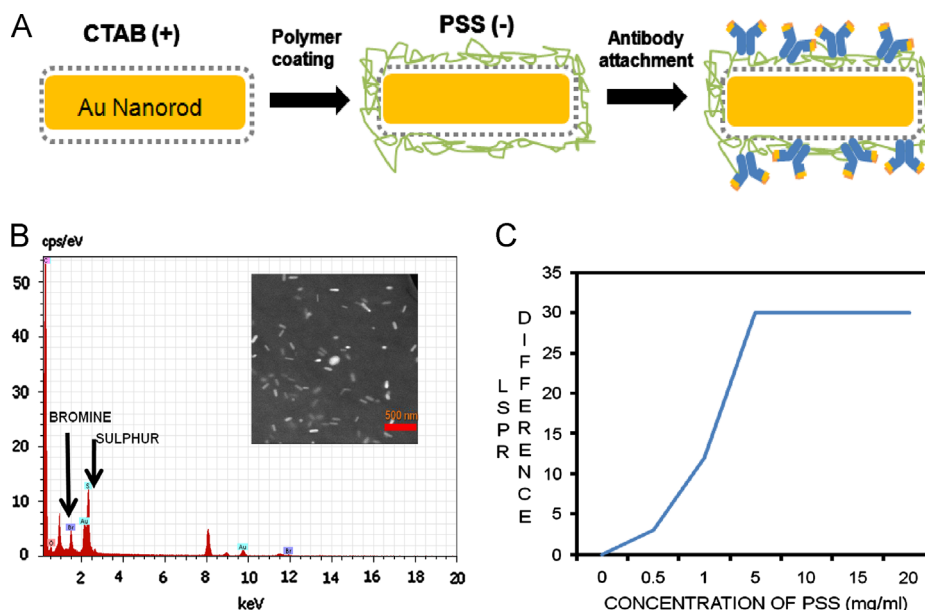
The unique optical properties of GNRs lead to strong absorption bands in the visible to infrared part of the spectrum. Fig. S1 shows a typical extinction spectrum of synthesized GNRs, where two peaks representing their transverse and longitudinal axes are present. The short axis exhibits a characteristic plasmon band at incident wavelength of  $\sim 520$  nm. The longitudinal peak at 760 nm is a stronger band corresponding to electron oscillation along the long axis. Scanning electron microscopy revealed a monodispersity of these rod shaped nanoparticles with  $40 \pm 7$  nm in length and  $10 \pm 3$  nm in width.

#### 3.1. Biofunctionalization of gold nanorods

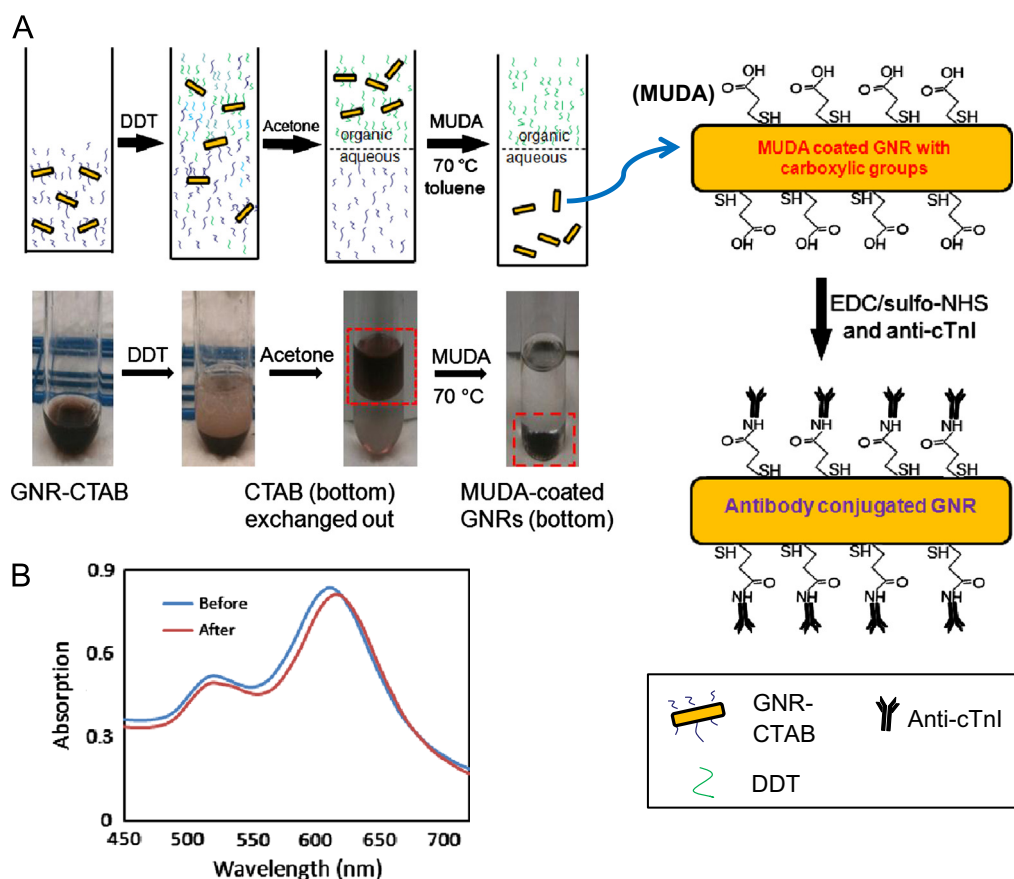
To construct a specific LSPR nanosensor, surface modifications of the GNRs were performed to facilitate functionalization with anti-cTnI molecules. Fig. 1 illustrates the electrostatic coating of GNRs with polyelectrolyte adsorbed on the surface. Since CTAB bilayer is positively charged, anionic polysodium 4-styrenesulfonate (PSS) can wrap around the CTAB–GNR surfaces by electrostatic self assembly, followed by adsorption of biomolecules. To confirm successful polymer coating, SEM was used to characterize the rod surfaces with chemical composition analysis by EDAX (Fig. 1B). Before poly-electrolytic wrapping, the CTAB-capped nanorods exhibited bromine as the dominant component. Incubation of the nanorods with 1 mg/mL PSS solution resulted in an increase in sulfur amount and diminished bromine in the EDAX spectrum. Specifically, bromine on the nanorod surface was decreased from  $2.64 \pm 0.1\%$  (wt) before coating to  $1.35 \pm 0.1\%$ , while the sulfur amount was increased from  $1.02 \pm 0.1\%$  to  $7.4 \pm 0.3\%$ , confirming the presence of an additional PSS layer. To further elucidate the effect of the PSS concentration on nanorod coating, GNRs were incubated with varying PSS concentrations up to 20 mg/mL and

UV–vis spectra were taken to monitor the polymer adsorption (Fig. 1C). A red-shift in the longitudinal plasmon band maxima was observed, which is consistent with change in the local refractive index from water to polyelectrolyte surrounding the nanorods. As more PSS molecules wrapped around the GNRs with increase in PSS concentration, the red shift became larger until 5 mg/mL, where the nanorod surfaces were completely covered by the electropolymeric coating. As such, higher concentrations did not cause further shift in the LSPR peak wavelength.

As a comparison to the electrostatic PSS adsorption, a surface modification to completely replace CTAB double layer by alkanethiol agents should provide a more robust functionalization. Here, we first used dodecanethiol (DDT) to remove CTAB bilayers because of high affinity of thiol to gold, followed by exchange of DDT molecules with MUDA containing carboxyl groups in the outer end (see Section 2). As shown in Fig. 2A, mixing the CTAB–GNRs with DDT resulted in a displacement of bound CTAB on the nanorod surface. Addition of acetone caused an aqueous-organic phase separation where gold NRs were extracted into DDT (top black portion), leaving CTAB in the bottom aqueous solution. The aqueous phase became clear, indicating that no GNRs remained. Further exchange of DDT coating by MUDA molecules caused an aggregation, indicative of MUDA self assembly monolayer on the surface of GNRs (MUDA–GNRs) which are insoluble in toluene. Black aggregates of MUDA–GNRs were successfully extracted from displaced DDT which remained in the upper organic phase. UV–vis spectra revealed that the MUDA exchanged GNRs effectively retained its longitudinal peak position and shape. The width of the LSPR peak shows no significant broadening as compared to the CTAB–GNR baseline. This indicates little nanorod aggregation during the process. Once coated by MUDA, the longitudinal SPR wavelength exhibited a shift of  $\sim 10$  nm from the baseline (Fig. 2B). This data corroborates with theoretical prediction as the refractive index of MUDA (1.463) is greater than that of CTAB bilayer (1.435 for a single layer). The pronounced plasmonic shift confirms the removal of CTAB by a single layer of MUDA coating on the nanorod. Similar to CTAB bilayer, the MUDA coating acts as a stabilizer to prevent aggregation. MUDA–GNRs are very stable for several months with little change in the shape and position of SPR band maxima. Additionally, the resulting carboxyl-terminated MUDA–GNR surfaces enable covalent binding of anti-cTnI molecules



**Fig. 1.** Electropolymeric coating of CTAB–GNRs. (A) Schematic showing the functionalization to construct a specific nanorod sensor. (B) EDAX analysis of the chemical composition on the GNR surfaces after PSS coating. Inset: electron microscopy of PSS coated nanorods. (C) Effect of PSS concentration.



**Fig. 2.** (A) Surface modification of CTAB–GNRs by phase transfer to displace CTAB bilayer by MUDA. Antibodies are then immobilized covalently through EDC/sulfo-NHS to the carboxyl-terminated GNR surfaces. (B) UV–vis spectroscopy of GNRs before and after MUDA exchange.

through EDC/NHS chemistry (Grabarek and Gergely, 1990; Staros et al., 1986). ELISA was performed to confirm the conjugation and functional activity of the antibody molecules attached onto the nanorods. While the gold nanoparticle only (negative control) showed a minimal signal, the antibody-conjugated gold nanorods demonstrated comparable signal intensities with the free-form antibody moiety (positive control).

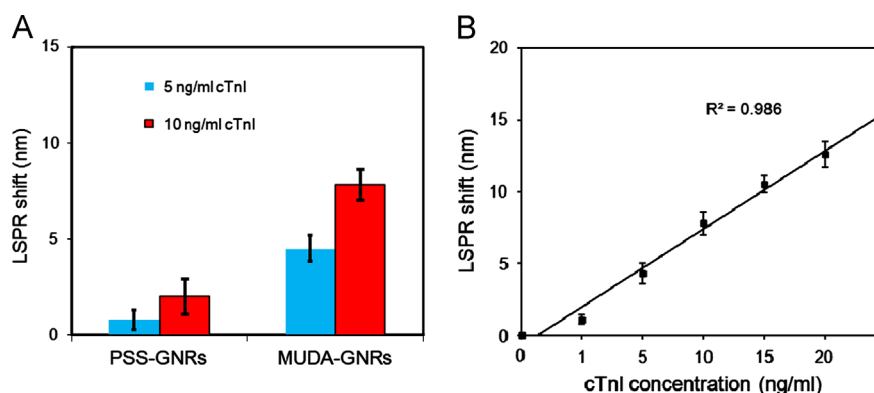
### 3.2. Comparison of cTnI biosensing performance

To evaluate the LSPR sensing performance for cTnI assay using the different routes of functionalization, spiked cTnI samples at varying concentration between 1 and 20 ng/mL were mixed with the GNR bioprobes respectively. UV–vis spectroscopy was used to monitor the red-shift in plasmon band maxima upon specific cTnI binding. Since the transverse peak is much less sensitive to local refractive index changes, longitudinal spectral shift was focused for LSPR biosensing. Fig. 3A shows the comparison of the cTnI assay using respective PSS- and MUDA-coated GNRs immobilized with anti-cTnI. For 5 ng/mL (150 pM) cTnI which is the detection limit of PSS–GNRs, the plasmon measurement only showed ca. 1 nm spectral shift. The MUDA–GNRs can overcome this limitation by replacing the CTAB molecules to result in a 5-fold increase to ca. 5 nm LSPR shift (Fig. S2). It was a similar case for 10 ng/mL cTnI assay. The improvement can be attributed to at least two factors. First, GNR surfaces modified with MUDA allows the covalent conjugate of anti-cTnI on carboxyl-terminated nanorods. Comparing to electrostatic adsorption on PSS–GNRs, covalent binding results in a surface functionalization with better biological activity and reliability in buffers containing high concentrations of ionic species. Second, as the transducer of a LSPR sensor, the

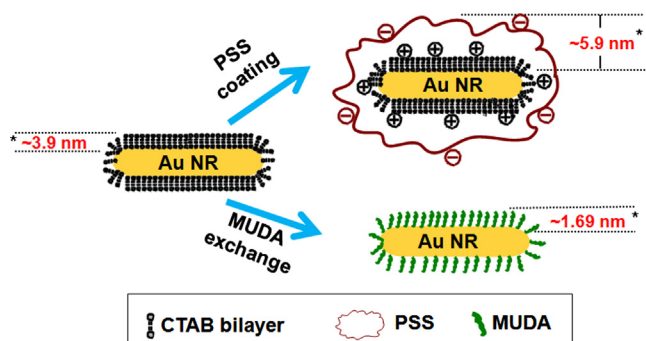
optical signal of nanorods arises from refractive index of the surrounding medium which can be altered by interfacial biological binding. This plasmon resonance sensitivity is highly distance dependent as shown in the following equation (Anker et al., 2008).

$$R = m\Delta\delta \left\{ 1 - \exp\left(-\frac{2d}{l}\right) \right\} \quad (1)$$

where  $R$  is LSPR spectral shift,  $m$  is the refractive index sensitivity,  $\Delta\delta$  is the change in the refractive index,  $d$  is the modification layer thickness on GNR surface, and  $l$  is the electromagnetic decay length. Clearly, distance from plasmonic nanostructures is critical in obtaining an optimal wavelength shift as the optical signature of receptor-analyte binding. Due to the evanescent nature of surface plasmon, the LSPR band maxima shift exhibits a characteristic decay with increasing distance from the nanorod surface. MUDA is a shorter alkanethiol agent ( $\sim 1.69$  nm; Yu and Irudayaraj, 2007) than the thickness of CTAB bilayer ( $\sim 3.9$  nm; Sreeprasad and Pradeep, 2011). As a result, replacement of CTAB by MUDA coating lead to a reduced distance of binding events to the rod surface. On the contrary, the addition of PSS coating on top of the CTAB–GNRs dramatically increases the distance by 51% to 5.9 nm (Fig. 4). Therefore, MUDA–GNRs were found to exhibit a significantly enhanced spectral sensitivity defined as relative shift in resonance peak wavelength with respect to the refractive index change of surrounding medium (RIU). Sucrose sugar solutions at different concentrations (0.2, 0.4, 0.8, 1, and 1.2 g/mL) were used to simulate increasing RI values (1.355, 1.374, 1.407, 1.420, and 1.428 respectively) (Yu and Irudayaraj, 2007). MUDA- and PSS-coated GNRs were probed in the sugar solutions sequentially to calculate the RIU by linearly fitting the red shift in longitudinal band maxima as a function of  $\Delta$ RI. As the coating thickness was reduced to 1.69 nm



**Fig. 3.** (A) Enhancement of LSPR sensitivity of cTnI assay using MUDA–GNRs over PSS coated nanorods. (B) Calibration curve of longitudinal spectral shifts as a function of cTnI concentrations based on MUDA–GNR sensor.

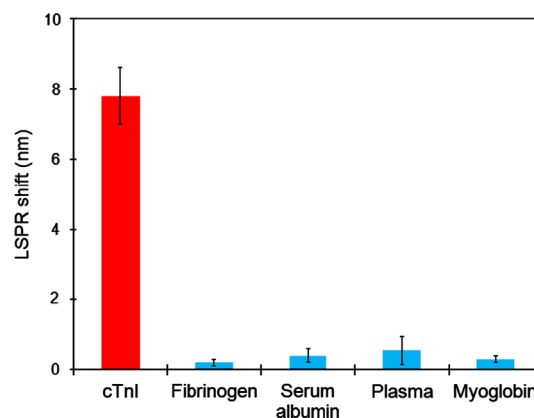


**Fig. 4.** Comparison of the thickness of PSS and MUDA modification layers to nanorod surface after electropolymer adsorption and CTAB exchange, respectively. \* the thickness is cited from studies by Yu and Irudayaraj (2007) and Sreeprasad and Pradeep (2011).

in MUDA–GNRs, the LSPR sensitivity was increased by 70% to 280 nm/RIU. This data clearly demonstrates that the sensitivity of LSPR sensing is strongly distance-dependent. In the actual cTnI sensing, this enhancement can lead to an excellent protein quantification with high sensitivity. Fig. 3B shows a linear relationship between the longitudinal spectral shift and cTnI concentrations in the sensing range ( $R^2=0.986$ ). The detection limit is ca. 1 ng/mL (30 pM) which is five times lower than that of PSS-coated GNR sensor.

### 3.3. Specificity of the gold nanorod probes for cTnI assay

Spontaneous reaction of thiolated molecules with CTAB-capped GNRs only leads to partial functionalization at the end faces of the rod-shaped nanostructure (Caswell et al., 2003). The remaining CTAB on the longitudinal sides, which is positively charged at physiological pH, can cause severe nonspecific binding problems. CTAB replacement in exchange of MUDA can fully activate the nanorod surfaces with carboxyl terminals for bioconjugates. This feature renders the latter method advantage in minimizing non-specific bindings. To ensure the LSPR shifts arise from specific binding of cTnI on the functional cTnI nanosensor, control experiments were carried out using irrelevant biomolecules such as fibrinogen, serum albumin, and normal plasma. Fig. 5 shows the resonance shift response when MUDA–GNR sensors were directly probed by various samples including myoglobin which is often recommended to be tested together with cTnI to improve diagnostic accuracy in clinics (McCord et al., 2001). While the cTnI sample at 10 ng/mL (median of the sensing range) caused ca. 8 nm red shift in the absorption peak, fibrinogen, serum albumin, plasma, and myoglobin samples at their physiological concentrations



**Fig. 5.** High specificity of the MUDA–GNR biosensor functionalized to conjugate with anti-cTnI molecules.

showed only a 0.2, 0.4, 0.5, and 0.3 nm shift respectively. This data suggests a negligible nonspecific binding, thereby realizing a label-free optical transduction of molecular recognition with high selectivity.

## 4. Conclusions

The CTAB bilayer tightly packed on the gold nanorods synthesized using seed-mediated growth method can be effectively exchanged by alkanethiol crosslinker such as MUDA via double phase transfer. This surface modification transforms nanorod surface to be carboxyl-terminated, enabling facile functionalization via covalent binding of biological moieties. Additionally, the displacement of CTAB by MUDA modification reduces the distance of binding events to the plasmonic rod surface. This results in a significant enhancement of the refractive index sensitivity of nanorods as an optical transducer, when compared to other functionalization methods such as additional electropolymer coating over CTAB–GNRs. This data also confirms the distance dependence of LSPR sensitivity to local refractive index change. The MUDA–GNR sensor exhibits an improvement in the sensitivity with a linear calibration curve of plasmon resonance shift vs. cTnI concentration in the sensing range. Detection limit was found to be ca. 30 pM cTnI. The complete removal of CTAB by MUDA facilitates full activation of the GNR surface to be functionalized, which also improves the specificity of the GNR sensor. Although physiological samples are mostly likely to be stable in pH and temperature, we expect our biosensor using MUDA-modified nanorods can better withstand environmental variations if any,

as compared to spontaneously electrostatic functionalization on CTAB-capped GNRs.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bios.2013.05.057>.

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