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Research Article

A Camera Phone Localised Surface Plasmon Biosensing Platform towards Low-Cost Label-Free Diagnostic Testing

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Developmental work towards a camera phone diagnostic platform applying localized surface plasmon resonance (LSPR) label-free sensing is presented. The application of spherical gold nanoparticles and nanorods are considered and assessed against ease of application, sensitivity, and practicality for a sensor for the detection of CCL2 (chemokine ligand 2). The sensitivity of the platform is compared with that of a commercial UV/Vis spectrometer. The sensitivity of the camera phone platform is found to be 30% less than that of the commercial system for an equivalent incubation time, but approaches that of the commercial system as incubation time increases. This suggests that the application of LSPR sensing on a portable camera phone devices may be a highly effective label-free approach for point-of-care use as a low-cost diagnostic sensing tool in environments where dedicated equipment is not available.

1. Introduction

Diagnostic testing aids the medical profession in a number of decision making processes. These include the decision as to whether to treat a patient or not when a threshold biomarker concentration is reached [1], refinement of patient management with respect to specific treatments, and methods, and in the selection of the most appropriate treatment for the patient. In the 1970's the arguments surrounding diagnostic testing related to the understanding of cost versus benefit, as the relatively high cost of tests and lack of knowledge in junior physicians led to excessive testing prior to new tests being properly evaluated [2]. In the following decades testing was regulated and adhered to basic standards, with tests being evaluated by consideration of specificity, accuracy, sensitivity, and social value [3, 4]. The core criterion of cost per test still remains however, and further development of low cost measurement is a compelling research field. The genomic revolution and the rise of "omic" sciences have led to the discovery of new biomarkers for diseases and their progression, resulting in a demand for new diagnostic tests. Patients benefit when tests are well understood, and detrimental issues are considered before testing occurs. A further deficiency is found where access to expert knowledge is required to conduct and evaluate tests leading to a clinical decision. The problem of testing in the developing world or remote area context is a process complicated by available equipment and personnel.

The "Lab on a chip" approaches provide a compact technology for user-friendly controlled testing. Design considerations for "lab on a chip" procedures are summarized from manufacture to disposal by Chin et al. [5]. In summary a device should be cheap to produce as well as dispose; rugged; possess temperature stability; allow passive fluid delivery/processing; deliver reproducible signal detection. In this scheme the problem of analysis of the output signal is not a consideration. This in turn places a requirement for expertise and training of the operator and raises the issue of

inaccurate analysis causing incorrect diagnosis precipitating inappropriate treatment and psychological stress in the patient; this additional consideration is rarely advanced in discussion of diagnostic system development. The literature provides many examples of "lab on a chip" processing using paper fluidics [6–13] and more conventional microfluidic devices using channels or printing methods for manual or passive sample processing and patterning of sensor chips [14–16]. Plasmonic platforms are widely used in the academic and industrial research environments [17], but are underapplied in low-cost diagnostic sensing. However, two recent trends, the widespread adaptation of cellular phones that contain cameras and the development of techniques to repeatedly fabricate metallic nanoparticles, motivate a re-evaluation of the potential of plasmonic sensing on a low-cost platform. Here we propose a sensing system in which the shift in the absorption spectrum of functionalized metallic nanoparticles is detected using a camera phone. The solution to the process of testing has to be holistic with each step being considered and with a minimum requirement for insitu expertise. Telemedicine is a field that is attracting more attention, where systems like "apps" for smart phones can be used to observe physical symptoms [18], further advice can be delivered as part of a telephone conversation [19] and patient information can be disseminated over a network [20]. Recent calls for innovation from the Grand Challenges program (Bill and Melinda Gates Foundation) recognize the potential for camera phone-based diagnosis, through advice "apps" and basic point of care diagnostic devices linked to camera phones [21]. A key problem recognized by the Foundation is that the purchase cost and energy consumption of a typical smart phone (necessary to run apps) are significantly higher than those of a basic cellular phone. With the ongoing reduction in the cost of optical and electrical components a basic camera phone could be considered the default low-cost cellular phone. It is possible to purchase a camera phone for under $20 with a 2 megabyte detector. A basic camera phone has many advantages:

(1) integrated photodetector (CCD/CMOS),

(2) primary form of telecommunications in sub-Saharan Africa where fixed lines have been superseded by mobile networks,

(3) solid state data storage,

(4) allows direct patient communication and text prompting as an aid to treatment,

(5) connectivity (USB, microSD, Bluetooth, text, mobile internet).

The concept of converting camera phones to diagnostic applications has seen limited application given the potential advantages; principally exploitation has involved the data communication aspect [22–24]. The examples found thus far include a microscope [25, 26], photography of wounds [27], and the paper-based assay approach of the Whiteside's group [28]. The latter example is the only case of the full potential of a camera phone being applied to telemedicine, where utilization bears the load in data acquisition through data transmission to a central processing node.

The user interface should as much as possible be based on a simple visual interface. This further reduces the user's required level of knowledge and reduces demands on literacy. Most basic mobile phones operate on a degree of visual recognition. Device operation can be reduced to following a list of symbols.

The extension to the principle of camera phone diagnostics that this paper will explore is the study of plasmonic-based assay principles using the phone as the data acquisition unit. Where localized surface plasmon resonances (LSPR) are considered, and absorbance change relative to concentration of analyte is the analytical measure. This is particularly true in the case of gold nanorods where the absorbance of the longitudinal resonance peak increases in proportion to the localized change in the dielectric constant caused by analyte binding at the particle surface [29]. LSPR approaches are a low-cost analytical technique. Gold nanorods can be readily synthesized using low-cost precursor materials, a very small volume of gold which provides sufficient nanorods for a very large number of assays. The challenge is to design an appropriate platform that can be adapted for immunological assays and which can be tailored to a specific disease by immobilization of appropriate antibodies. LSPR enjoys the virtue of being a label-free technique where signal amplification is not required through coupling of antibodies to luminescent labels or chemical reagents in colorimetric analysis.

2. Methods

2.1. Nanoparticles. Two types of gold nanoparticles were used in experiments, spheres, and nanorods. Spherical citrate-capped particles were synthesized in house using the following protocol adapted from [30], all chemicals purchased from Sigma Aldrich. 80 mL of 0.01% (w/v) $HAuCl_4$ is transferred to a 500 mL flask and magnetically stirred. A reducing mixture was prepared consisting of 4 mL 1% (w/v) trisodium citrate dihydrate, 0.2 mL 1% tannic acid, and 15.8 mL distilled water. Both solutions were heated to 60°C, and reducing solution is rapidly added with stirring to $HAuCl_4$ solution. After 1 h, the solution is cooled. Mono-dispersed colloidal gold nanoparticles were obtained. Particles could be stored for up to 6 months at room temperature without significant aggregation. Previous work using this protocol in our group gives a single localised surface plasmon extinction peak at 514 nm. Gold Nanorods were synthesised and kindly provided for this work by the groups of Professors Lennox and Reven at McGill. Nanorods were of aspect ratio 3 that has recently been suggested as the ideal aspect ratio for LSPR sensing [29]. Rods were capped and stabilised with CTAB. Rods possessed a longitudinal LSPR peak at 700 nm and a transverse peak at 534 nm.

2.2. Instrumentation. The basic instrumentation for the device is a steel cylinder housing a tri-colour LED (Digikey) power by rechargeable batteries and camera phone (Motorola razor). The tricolour LED provides blue, green, and red illumination dependent upon application of the 1.5 V supply from batteries. For these experiments only

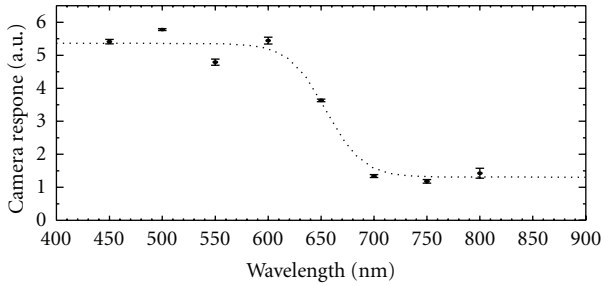

Figure 1: Spectral range of CMOS camera phone.

the green and red channels were used at 520 nm and 610 nm, respectively. Batteries were recharged using a solar power recharger of which there are many on the market, but we opted for a home-built system that costs $20 to fabricate. A basic schematic is provided in Figure 2(d). In advance of nanoparticle testing the spectral range of the camera phone was measured. This was accomplished using a Xenon lamp and monochromator with collimated output to project light of known wavelength from 450–850 nm onto the camera phone objective. Five images were taken at each wavelength and transferred by microSD card to a laptop for intensity analysis of images achieved with Image J (available from NIH) and graphs plotted using Matlab or MS Excel. The CMOS detector of the camera phone is observed to be most sensitive between 450 and 600 nm as expected for a device designed to capture images in the visible region of the spectrum. The decline in sensitivity is linear between 600 to 700 nm, and no observable difference could be detected in images from 700 nm to 850 nm (see Figure 1). In order for the principle of camera phone detection to function, assays must have observable spectral changes (absorbance or scattering) within the visible range. The initial proof of concept device allows for single-channel imaging, but future work will consider multiple channels (making use of the camera lens to resolve multiple sample wells).

2.3. Image Collection and Processing. Images are first collected and transferred from the camera using either a bluetooth connection to a laptop or a miniSD card. Basic image processing software (Adobe Photoshop, GNU GIMP or MS PowerPoint) was applied to arrange the images in order of highest concentration to lowest, and they were then saved as a JPG format image file. Subsequently the combined images were loaded into ImageJ (NIH), and the average intensity of each image spot was calculated using the fixed area selection tool. ImageJ logs each measurement, and the area of selection and the data can be copied into other software packages (Excel or Matlab) for graphing and further processing.

2.4. Experimental. Initial studies applied functionalized gold nanoparticles with anti-CCL2 bound to the particles surface in aqueous solution. The first consideration was with regard to the most appropriate type of bioassay to attempt. A common biomarker for inflammation and breast cancer was chosen (CCL2) with appropriate capture and reporter antibodies (BD biosciences). Binding in a nanoparticle assay is observed through absorbance or peak wavelength shift. The simplest assay to implement is the binding of functionalized nanoparticles to antigens (see Figure 2(a)) causing a localized refractive index change and thereby providing the optical readout. Amplification of the signal is simply achieved by the addition of a secondary reporter antibody bound to a gold nanoparticle. In this paper the dual nanoparticle assay is applied as it provides a clear signal enhancement method, over the direct assay.

Two batches of nanoparticles were functionalised with a capture and reporter antibody separately. Monoclonal antibodies cross-specificities were previously assessed by the Juncker's Group at McGill and were found to bind different epitopes of CCL2. The purpose was to create two populations of nanoparticles with specificity conferred by the antibodies for different epitopes of CCL2. For capture antibody functionalisation, 1500 μL of nanoparticles was mixed with stock anti-CCL2 to give a concentration of 3.33 μg/mL. Reporter antibody was used to functionalise the second batch of nanoparticles (1.5 mL) with a protein content of 0.66 μg/mL. Batches were prepared and incubated for 2 hrs before use and brought to 25°C prior to use. Functionalisation of nanoparticles and rods relies upon direct physical adsorption to the surface. To prevent nonspecific binding, PEGylation of the surface between absorbed antibodies was performed. 5 μL of 5 mM PEG2000 thiol (Sigma Aldrich) was added to 1.5 mL batches of nanoparticles and incubated at 25°C for 1 hour, so that PEG would be inserted between adsorbed antibodies. For both reporter and capture antibody ten batches of each were prepared in advance and stored at 4°C until required. All biomolecules were stored when not in use at −20°C.

To perform the direct assay 5 cuvettes were taken and 400 μL of capture antibody functionalised nanoparticles was pipetted into each. 5 μL of different CCL2 concentrations (serial dilution from 1 to 0.05 μg/mL) was pipette into each cuvette and stirred vigorously. The assay was repeated 3 times at each concentration with fresh nanoparticles.

The dual assay used the same CCL2 concentration range, but only 200 μL of capture antibody nanoparticles was added to cuvettes. 5 μL of antigen solution was added using the same concentration range as for the direct assay and stirred. After 1 hr incubation at 25°C, 200 μL of reporter antibody nanoparticles was added to the cuvettes with a further incubation of 1 hr. This maintained a consistent volume; nanoparticle concentration was also fixed at 5 ng/mL. Where gold nanorods were applied the same concentration of 5 ng/mL was used and functionalisation by direct physical adsorption follows the same protocol as for preparation of the direct assay nanoparticles. Gold nanorods assays were realised using the direct assay protocol without additional reporter particles. The UV/Vis comparative assay which used the dual assay protocol but over the concentration range 300 to 2 ng/mL.

In both direct and dual assay approaches, solutions were placed in custom 1 cm cuvettes and placed into the steel housing of the device, and images were captured of the transmitted light from the LED. The dark background on images

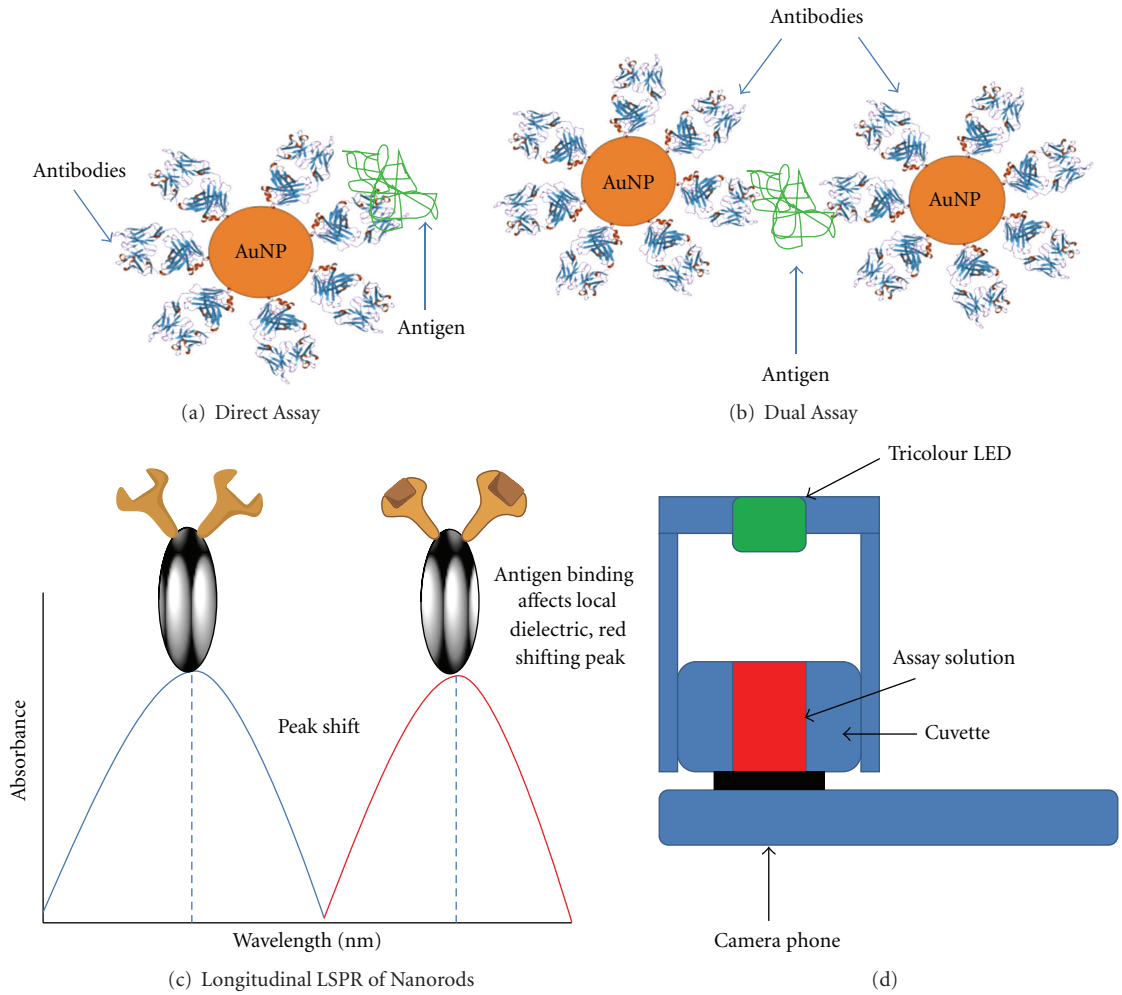

Figure 2: Summary of nanoparticles assay approaches. (a) Direct single nanoparticles assay, (b) dual reporter and capture assay, (c) direct nanorod assay with representation of peak shift and absorbance change as a guide (d) indicates the basic experimental set up for both assays where a custom housing supporting the tri-coloured LED and cuvette with nanoparticle assay is placed upon the camera phone lens system for image acquisition.

is created by the walls of the cuvette acting as an aperture stop.

In these experiments only the dual assay is discussed as the direct assay with spherical nanoparticles using the camera phone as the detector does not produce a significant change in absorbance below 1 μg/mL. The dual assay has an obvious enhancement in absorbance as there is both a large change in local dielectric environment caused by the additional biomolecules involved in the dual assay (2 classes of antibodies plus CCL2) and the close proximity of an additional gold nanoparticle that will increase the absorbance of the plasmonic mode. The result of applying a reporter nanoparticle was that consistent calibration plots could be generated. This was not possible with the direct assay below 1 μg/mL, hence it is excluded from further consideration. The reason for the direct assay showing no significant change in absorbance below 1 μg/mL is a function of the CMOS detectors sensitivity to small changes in the transmitted light collected as an image and the lack of a plasmonic enhancement as discussed for the dual assay. Error in protocol for direct assay is excluded as it performed excellently with gold nanorods.

The time required to perform the dual assay is an important factor to consider. If the time required is prolonged (in excess of minutes) this limits the number of tests over a given time period. The ideal situation is a test where sampling and results occur within a few minutes to an hour period. Figure 3 and Table 1 show the results for a dual particle assay for CCL2 where multiple assays were run at different incubation periods (period after addition of reporter antibody). The purpose is to resolve the issue of the ideal time period for achieving the most favorable figures of merit versus the time required to conduct the assay. The quantification range (0.099 to 1 μg/mL) (18 hr incubation) is compatible with clinical study of CCL2 with relevance to multiple sclerosis, prostate, and breast cancer [31–33]. For future studies an incubation of at least 1 hr is recommended.

To compare the relative performance of the camera phone platform the same assay was performed using a UV/V

Table 1: Summary of CCL2 assay performed over different incubation periods.

Time	Sensitivity (ΔA/Δ[C])	Detection limit (μg/mL CCL2)	Standard error	Standard deviation	Number of samples
2 mins	0.0768	0.723	0.0107	0.0186	10
1 hr	0.5376	0.087	0.0087	0.0153	10
2 hr	0.5707	0.115	0.0131	0.0223	10
18 hr	0.8	0.099	0.0147	0.0254	10

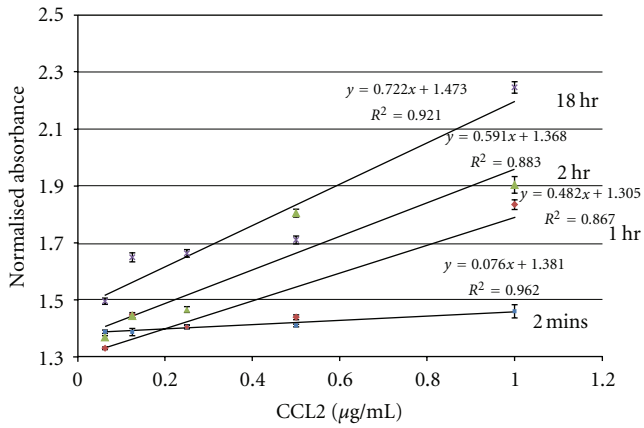

Figure 3: Comparison of incubation time and assay performance. Larger changes in absorbance can be achieved by longer incubation times, allowing improved resolution at lower concentration.

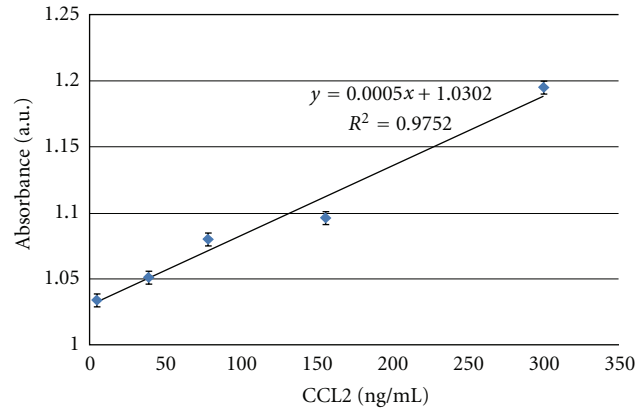

Figure 4: Calibration Curve for Assay performed on UV/Vis spectrometer.

is spectrometer (Varian Cary 1) using a quartz cuvette (1 cm pathlength). Figure 4 shows the calibration curve for the dual nanoparticle assay approach.

As expected a more stable and accurate instrument improves assay performance over the comparable experiment with the camera phone; this is demonstrated by the improved sensitivity of 0.78 (ΔA/Δ[C]). This level of sensitivity would require incubation for 18 hr with the camera phone assay approach to achieve parity. The clear compromise in application of the camera phone method is detector sensitivity and the required increase in incubation time to achieve a comparable sensitivity with UV/Vis spectroscopy. It should be appreciated that a sensitivity comprise is a function of detector cost, as it is the stated intention that the camera phone platform be of minimal cost, an increased incubation time is an acceptable trade-off.

2.5. Assay Complexity and Sensitivity. Though the dual particle solution assay performs well with spherical gold nanoparticles, if greater sensitivity is required it is possible to apply gold nanorods, with the red LED channel to improve resolution. Figure 5 illustrates the steps required to generate the absorbance changes in images and to derive the calibration curve. CCL2 is again used as the antigen and capture antibody is absorbed onto the nanoparticles. Addition of nanoparticles of both types with a secondary reporter antibody for CCL2 (conc. 0.66 μg/mL) was used as an enhancement strategy, using the same antibody concentrations as previously used to functionalize spherical particles. A serial dilution of CCL2 antigen was prepared and added to aliquots of the nanoparticles (volume 500 μL) (spherical and rods separately), and an equal volume to the starting capture particle solution was added (500 μL). The incubation period was 30 mins at 25°C. Spherical particles were illuminated by using the green illumination of the LED (~520 nm) and a red illumination of the LED (~610 nm) for gold nanorods. Note that the dark background of the images is caused by the walls of the cuvette creating an aperture stop in the field allowing only measurement of light that has passed through the nanoparticle/rod solution. Each image presents light from the LEDs passing through the cuvette with either nanoparticles (green images) or rods (red images). Each concentration was measured three times and equates to 3 images in each row. To allow easier data processing images are combined to produce the compound images of Figure 5. These are processed within Image J as indicated in Figure 5.

Figure 5 illustrates the improvement in sensitivity and hence resolution that can be achieved by application of the gold nanorods over spherical nanoparticles. For solution-based assays the nanorod provides a more attractive plasmonic material to apply to assay development particularly as the nanorod longitudinal resonance (~600 nm) is well matched to the LED source. A comparison of sensitivity shows that nanorods have a greater sensitivity (0.5625 ΔA/Δ[C]) over gold nanoparticles sensitivity of 0.375. This test suggests that future low-cost diagnostics should investigate the application of gold nanorods as they have a superior extinction coefficient in comparison to nanoparticles and improve the signal to noise ratio for the detection of biomolecules with this device.

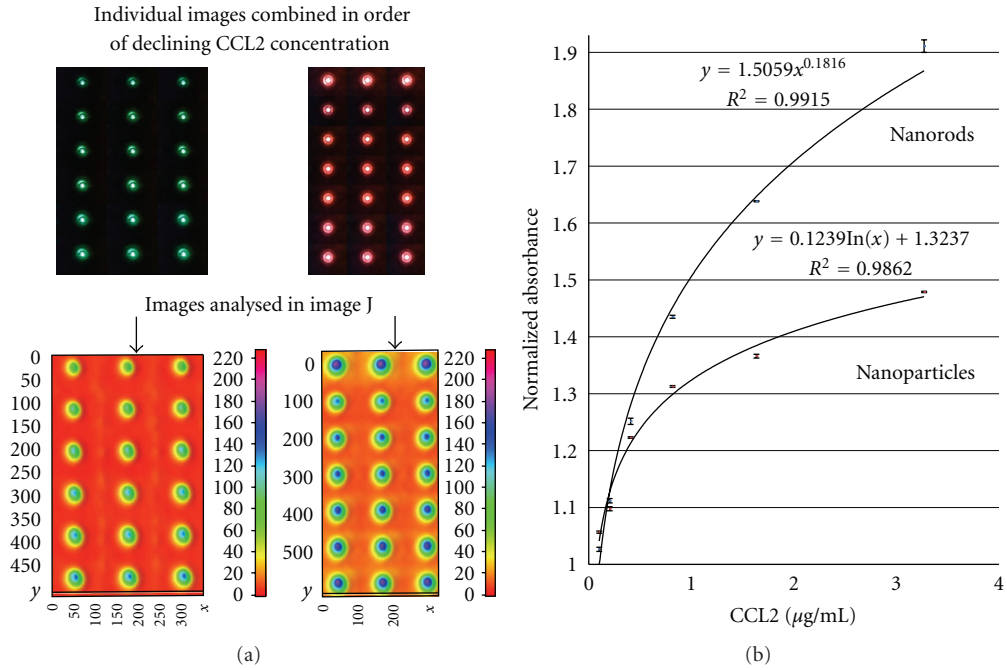

FIGURE 5: Comparison of CCL2 absorbance change versus concentration using spherical and rod-shaped gold nanoparticles. Images of transmitted light were captured 3 times for each concentration and placed in a row. Images were then combined in column to produce a microtiter array pattern of declining CCL2 concentration. Intensities of each concentration for both nanoparticle and nanorod assay were assessed within Image J for calculation of absorbance.

3. Conclusion

The application of a camera phone has been explored by solution-based assay approaches and with reporter antibody enhancement, where close interaction of the nanoparticles electrical fields caused by antigen-mediated separation distance increased the absorbance of light at measured wavelengths. The assay is shown to perform in a clinically relevant concentration range for analysis of CCL2 (0.099 to 1 μg/mL) with a detection limit of 0.099 μg/mL. Incubation time can be selected depending upon the sensitivity required of the assay; either 1 hr or 18 hr seem most appropriate from the results. If the analytical threshold for treatment is in the mid range of the dynamic range, an 18 hr incubation period would allow a greater sensitivity. The prolonged incubation period for the increase in sensitivity is caused by the combination of the spherical nanoparticles and the detector. Gold nanorods are an excellent choice for the optical mediator in this sensing platform as the degree of absorbance change even off peak resonance is greater than spherical nanoparticles, improving the performance of the CCL2 assay, and should provide a solution to the presently long incubation time. The use of a camera phone and plasmonic nanoparticles suggests that a range of antibody-based assay could be transferred readily to this easy to use diagnostic platform. The application of a tri-colour LED also offers advantages of energy efficiency and wavelength selection. The goal for future work is to develop the platform to allow the analysis of multiple channels rather than a single channel and to integrate the LED light source into low-cost package to which the camera phone could also be attached.

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