# Detection of Escherichia coli O157:H7 Using Gold Nanoparticle Labeling and Inductively Coupled Plasma Mass Spectrometry

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# Detection of *Escherichia coli* O157:H7 Using Gold Nanoparticle Labeling and Inductively Coupled Plasma Mass Spectrometry

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**O157:H7 is a serotype of enterohemorrhagic *Escherichia coli* (EHEC) and one of the major causes of food-borne illness. Protection of food safety against bacterial contamination and rapid diagnosis of infection require simple and fast assays for detection of bacterial pathogens, including *E. coli* O157:H7. We describe here a rapid and sensitive assay for the *E. coli* O157:H7 bacteria by using antibody affinity binding, gold nanoparticle (Au NP) labeling, and inductively coupled plasma mass spectrometry (ICPMS) detection. Taking advantage of the signal amplification property of Au NPs and the high sensitivity of ICPMS, the assay was able to detect as few as 500 *E. coli* O157:H7 cells in 1 mL of sample (500 CFU/mL). Tests with nonpathogenic *E. coli* (DH5α, ATCC35218, and ATCC25922) showed high specificity of the assay for *E. coli* O157:H7. Each assay was completed within 40 min. Demonstration of this assay for *E. coli* O157:H7 suggests its potential for detecting a variety of bacterial pathogens.**

The analysis of pathogenic bacteria is vital for protection of food and water safety, health surveillance, and clinical diagnosis. Among more than 100 known serotypes of *E. coli*, O157:H7 is a notorious pathogen confirmed in many outbreaks of food-borne illnesses.[1,2] It causes bloody diarrhea, hemorrhagic colitis, and occasionally hemolytic uremic syndrome (HUS, a type of kidney failure). An infection dose as low as ~100 cells can lead to disease or even death, especially in children, elderly, and immunocompromised people.[1] Therefore, clinical diagnosis as well as the food and water industry continue to demand fast and sensitive assays for *E. coli* O157:H7.[3−5] Conventional methods for detection of pathogenic bacteria include culture techniques,[6] polymerase chain reaction (PCR),[7−9] and enzyme-linked immunosorbent assays (ELISAs).[10,11] To improve the sensitivity and speed of analysis, much recent effort has focused on the use of fluorescence nanoparticles[12] or nanovesicles,[13] quantum dots,[14−16] bioluminescence,[17,18] mass spectrometry,[19] infrared (IR) spectrometry,[20,21] surface enhanced Raman spectrometry (SERS),[22,23] Rayleigh scattering spectrometry,[24] piezoelectric biosensors,[25,26] and amperometric biosensors.[27] The objective of the present study was to develop a new analytical strategy for bacterial detection that could achieve high speed and high sensitivity by taking advantage of antibody affinity, gold nanoparticle (Au NP) labeling, and inductively coupled plasma mass spectrometry (ICPMS) detection.

ICPMS is one of the most sensitive techniques for trace element analysis, providing large dynamic range, low detection limits, and multi-element and rapid analysis capability.[28,29] Re-

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cently, the use of elemental tags and inorganic nanoparticles has also made ICPMS amenable for analysis of biomolecules.[28–34] Although inorganic nanoparticles, such as Au NPs, have been applied as detection and imaging probes,[35] they have not been demonstrated in ICPMS assays for whole bacterial cells. We show here for the first time an affinity assay for bacterial cells using nanoparticle labeling and ICPMS detection.

To demonstrate the proof of principle, we chose *E. coli* O157:H7 as the target analyte. A monoclonal antibody for *E. coli* O157:H7 is conjugated to gold nanoparticles (Au NPs, 10 nm diameter), and these Au NPs serve as affinity probes to recognize the *E. coli* O157:H7 target. Subsequent detection of Au NPs by ICPMS leads to quantitative analysis of the bacterial cells. Because ICPMS measures Au elemental ions produced by Au atoms and a 10 nm-diameter Au NP contains ~30 000 Au atoms,[31,34] the use of 10 nm Au NPs could potentially enhance the signal by up to 30 000-fold, thereby dramatically improving the sensitivity of the assay.

## EXPERIMENTAL SECTION

**Chemicals and Materials.** Mouse monoclonal antibody (mAb) against *E. coli* O157:H7 was purchased from Biodesign International (Meridian Life Science). Biotin-conjugated rabbit polyclonal antibody to *E. coli* O and *E. coli* K was obtained from Abcam (product no. ab33839). *E. coli* O157:H7 cultures (strain ADRI V241) were provided by the Agri-Food Laboratories Branch, Alberta Agriculture and Rural Development (Edmonton, Alberta, Canada). *E. coli* DH5α, ATCC35218, and ATCC25922 were obtained from the American Type Culture Collection. A solution of gold standard was purchased from Agilent (Multi-Element Calibration Standard-3, 10 $\mu$g/mL). Solutions of gold nanoparticles (Au NPs) (10 nm in diameter, $5.4 \times 10^{12}$ Au NPs per mL) and streptavidin-labeled Au NPs (10 nm in diameter, $1.4 \times 10^{13}$ Au NPs per mL) were purchased from Sigma. Bovine serum albumin (BSA) was also purchased from Sigma. Phosphate buffered saline (PBS) 10× solution and nitric acid (Optima grade) were obtained from Fisher Scientific.

**Bacteria Culture and Plate Counting.** The culture conditions were previously described in detail.[7] Briefly, *E. coli* O157:H7 was grown in tryptic soy broth (TSB) at 37 °C with shaking (125 rpm). To count the number of bacterial cells, cultures were serially diluted with sterile water, and 100 $\mu$L of the selected dilution was mixed with warm tryptic soy agar (TSA) and poured to plates into triplicate. Plates were incubated at 37 °C for 24 h. For calculation of the numbers of colony-forming units per mL (CFU/mL), dilutions showing between 30 and 300 colonies on TSA were used.

**Preparation and Characterization of Antibody-Modified Au NPs.** *Direct Modification.* Anti-*E. coli* O157 mAb was modified onto Au NPs according to the literature procedures.[36] A measured amount of mAb was added to 1 mL of Au NP solution (undiluted) at pH 9.0. After incubation at room temperature for 30 min, the mixture was passivated and stabilized with 500 $\mu$L of a 5% BSA solution for 1 h. The final solution was centrifuged at 17 000*g* for 1 h at 4 °C, and the supernatant was removed. Centrifugation for 1 h was sufficient to separate the Au NPs from the solution, as monitored by the color of the solution. We found that after centrifugation for more than 40 min, the solution became colorless and transparent, indicating that Au NPs settled in the bottom of the tube. The Au NP pellet was redispersed in 1 mL of PBS buffer with 0.5% BSA at pH 7.4 after washing with PBS buffer 2 times. The modified Au NPs solution could be stored at 4 °C for more than 1 month. The loading of mAb onto Au NPs was determined by a modified colorimetric method.[36] In this experiment, various amounts of mAbs were added to 1 mL of Au NP solutions ($5.4 \times 10^{12}$ Au NPs per mL) at pH 9.0. After 30 min incubation at room temperature, NaCl was added to each solution to a final concentration of 0.3 M, and the final color of each solution was observed and recorded using a digital camera.

*Modification through Streptavidin−Biotin Interaction.* A total of 7.0 $\mu$g of polyclonal antibody (pAb) and 200 $\mu$L of streptavidin-labeled Au NP solution ($1.4 \times 10^{13}$ Au NPs per mL) were added together and diluted to 1 mL with 1× PBS buffer containing 1% BSA. The mixture was incubated at room temperature for 30 min and then stored at 4 °C.

**Incubation of Cells with Antibody-Modified Au NPs.** Anti-*E. coli* O157:H7 mAb-modified Au NPs (10 $\mu$L) were added to 100 $\mu$L of sample solution containing $0-5 \times 10^7$ CFU/mL of *E. coli* O157:H7, suspended in 1× PBS with 0.5% BSA. The mixtures were incubated at room temperature for 20 min, followed by washing 3 times with 1× PBS buffer (centrifugation at 17 000*g* for 1 min). The separation of cells (micrometer size) from the culture medium and washing solution was readily and commonly achieved using a 1 min centrifugation. Finally, the cell pellets were redispersed and digested in a 200 $\mu$L solution of 1% $HNO_3$ with 1% BSA for digestion. The digest was introduced into the ICPMS to detect Au at $m/z$ 197. For each sample and calibration solution, triplicate analyses were performed using ICPMS.

To demonstrate specificity, a control experiment was performed in the same manner as described above, except that *E. coli* O157:H7 cells were replaced by nonspecific *E. coli* cells (DH5α, ATCC35218, or ATCC25922). To determine the detection limit, replicate analyses of blanks were performed. Six replicates of blanks were treated the same way as for *E. coli* O157:H7, and the standard deviation was calculated from 18 analyses (triplicate ICPMS analyses of each blank).

**ICPMS Analysis.** An Agilent 7500cs octopole reaction system ICPMS, operated in the helium mode, was used for the elemental analysis of Au NPs. The operating parameters of ICPMS are summarized in the Supporting Information, Table S1. A 20 $\mu$L sample was injected using a Rheodyne six-port injector (model 7725i) to a 1% $HNO_3$ carrier stream. Detailed information about tuning and operating conditions was described previously.[34]


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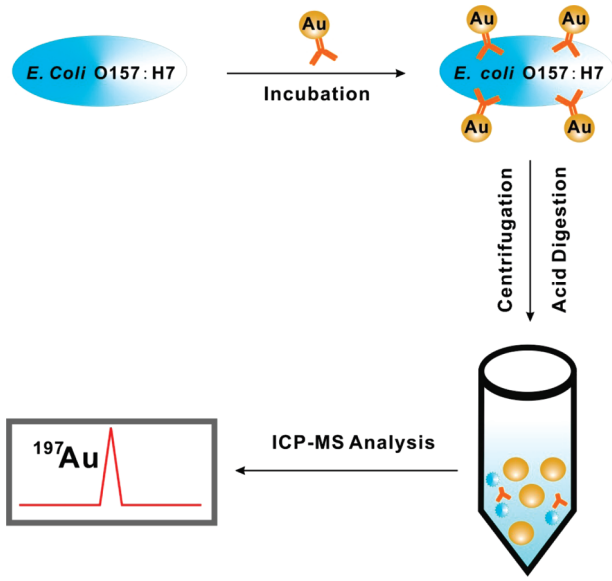


**Figure 1.** Schematic diagram showing the principle of the assay. The *E. coli* O157:H7 cell was incubated with antibody-conjugated gold nanoparticles (Au NPs, shown in gold). The unbound Au NPs were separated from the cell complex by centrifugation. The cell pellets containing Au NPs were digested with 1% nitric acid after washing, and the solution was analyzed by ICPMS. The intensity of the ICPMS measurement of Au at *m/z* 197 corresponds to the concentration of *E. coli* O157:H7 cells in the original sample.

**Caution.** *E. coli* O157:H7 is pathogenic and should be handled in a Level 2 biohazard hood.

## RESULTS AND DISCUSSION

The principle of the assay is schematically shown in Figure 1. To carry out an analysis, the antibody-conjugated Au NPs are added to a sample solution. The target bacterial cells bind with the antibody to form affinity complexes, linking the cell, antibody, and Au NPs. The mixture is centrifuged to separate the Au NPs bound to the cells from the unbound Au NPs. The fraction of the cell-bound Au NPs is then acid-digested and quantified by the determination of Au using ICPMS. The key components in developing this assay include the conjugation of antibodies to Au NPs, the specific binding of these conjugates to the bacterial cells, and sensitive detection of Au NPs using ICPMS. Each of these components contributes to the sensitivity and specificity of the assay. These components are optimized and discussed below.

**Characterization of Antibody-Modified Au NPs.** To attach antibodies to Au NPs, we adapted a well-documented technique of protein adsorption onto Au NPs.[35,37] The adsorption process is dependent on pH and the amount of protein loading. Consistent with the reported observations,[37] we found that a pH value of 9.0 was suitable for achieving Au NP modification with monoclonal antibody against *E. coli* O157:H7. To monitor the amount of antibody loading on the Au NPs, we used a simple colorimetric assay. In the absence of antibody modification, Au NPs in water appear red (Figure 2, far left tube). The addition of 0.3 M of NaCl to this Au NP solution causes an immediate color change from red to blue (Figure 2, far right tube). This color change is due to flocculation of nanoparticles. With the addition of antibody to the

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**Figure 2.** Result of antibody loading test. The far left tube contained Au NPs in water with no salt or antibody added. To the other tubes containing the same amount of Au NPs, varying amounts (0–10 $\mu$g) of antibody and 0.3 M NaCl were added.

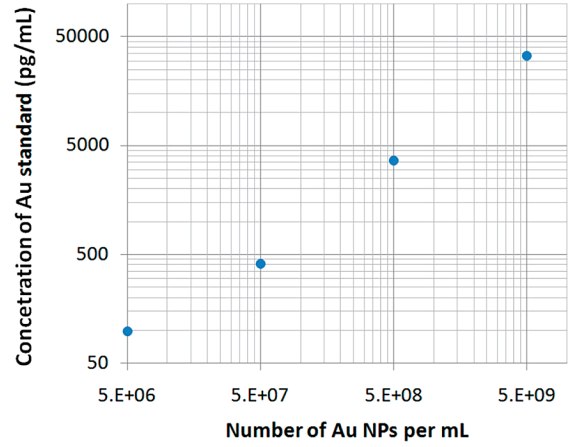


**Figure 3.** ICPMS analyses of Au NPs, calibrated against Au standard solutions. Au NP solutions containing varying amounts of gold nanoparticles ($5 \times 10^6$/mL to $5 \times 10^9$/mL) and Au standard solutions were analyzed by ICPMS. The concentration of Au NPs (number of Au NPs per milliliter) and Au standard solutions (picograms per milliliter) that resulted in identical signal intensities were correlated. Error bars (1 standard deviation from triplicate analyses) are smaller than the size of the symbol.

Au NP solution, the electrolyte-induced flocculation was reduced or eliminated. This is due to the presence of antibodies on the surface of Au NPs. With an increasing amount of antibody, the color of the Au NP solution was reversed back to red, as shown from right to left in Figure 2. An amount of 7 $\mu$g/mL was selected since we found that the Au NPs were well-stabilized when the amount of antibody was greater than 6 $\mu$g/mL. This amount (7 $\mu$g/mL) corresponds to ~5 protein molecules on each Au NP.

The Au NPs with antibody modification were further characterized using ICPMS. Previous work has shown that Au NPs could be quantified by ICPMS and that the atomization efficiency of ICPMS for nanoparticles is the same as for Au ions in solution.[30,34] Thus, by calibrating the number of Au NPs against the concentration of Au in standard solutions (Figure 3), we are able to measure the amount of Au atoms in each Au NP. Our results show that each Au NP (10 nm size) contained 21 400 Au atoms, which is consistent with other reports.[31,34]

**Detection of *E. coli* O157:H7 by ICPMS.** Using monoclonal antibodies attached to Au NPs as affinity probes to recognize *E. coli* O157:H7, we have developed a sensitive assay for this pathogen. Figure 4 shows typical results from one set of experiments with different concentrations of *E. coli* O157:H7 cells, ranging from 50 to $5 \times 10^6$ CFU/mL. The signal intensity increases with increasing cell concentrations. A detection limit

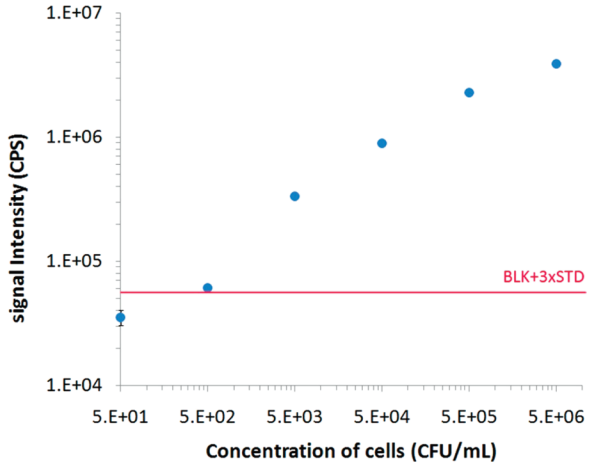


**Figure 4.** The measured signal intensity as a function of the concentration of *E. coli* O157:H7 cells in water samples. Error bars represent 1 standard deviation from triplicate analyses.

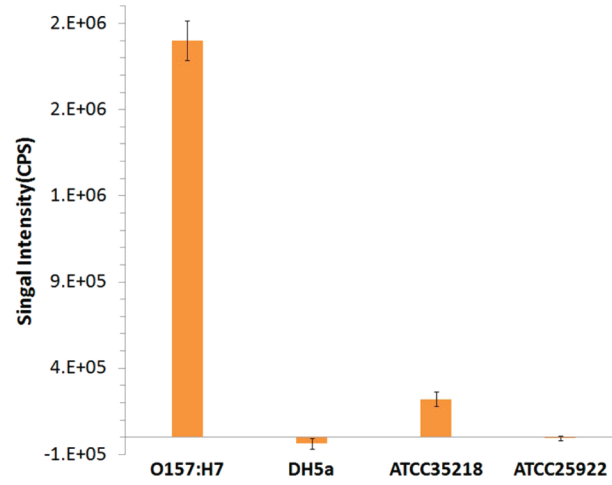


**Figure 5.** Results of specificity test. Samples contained either *E. coli* O157:H7 cells or one of the nonspecific *E. coli* cells (DH5α, ATCC35218, or ATCC25922). Concentrations of bacterial cells were $5 \times 10^5$ CFU/mL. Error bars represent 1 standard deviation from triplicate analyses.

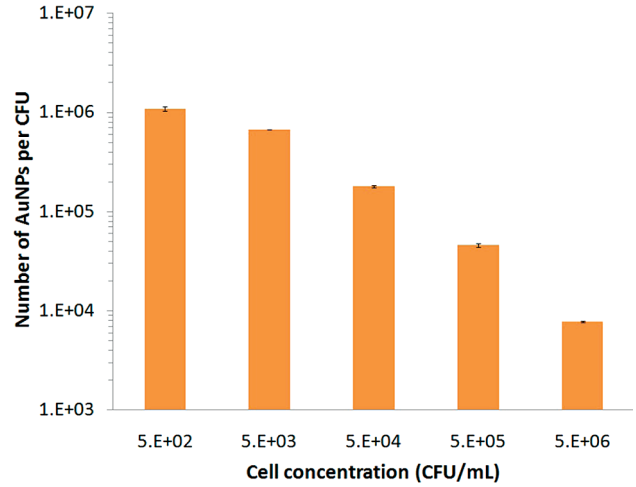


**Figure 6.** Average number of Au NPs bound to each CFU as a function of increasing concentrations of *E. coli* O157:H7 cells. Error bars represent 1 standard deviation from triplicate analyses.

of 500 CFU/mL was achieved. This conservative estimate was based on 3 times the standard deviation of the background plus the mean blank values from triplicate analyses of each of 6 blanks. The linear dynamic range was between 500 and $5 \times 10^5$ CFU/mL with a linear correlation $r = 0.964$.

The assay procedures involve a short incubation, a simple centrifugation to separate the cells, acid digestion, and ICPMS analysis. Because both *E. coli* O157:H7 cell labeling and ICPMS detection require only minimum sample preparation, the assay is simple and fast, taking less than 40 min for each sample: 20 min for incubation, <15 min for washing and acid digestion, and <5 min for ICPMS detection. Triplicate ICPMS analyses showed a relative standard deviation (RSD) of <5%, and triplicate sample preparations exhibited RSD of <10%.

The specificity of this assay is mainly dependent on the antibodies used. *E. coli* O157:H7 contains two specific antigens: O polysaccharide (O157) and flagellum protein (H7). The antibody we used specifically recognizes the lipopolysaccharides (LPS) oligosaccharide region of the cell and has no reactivity with most other *E. coli* serotypes, such as O111, O125, O20, O155, and K12. However, any nonspecific binding or adsorption of Au NPs would produce background signals. To test the specificity of the assay, we used several nonspecific *E. coli* cells, DH5α, ATCC35218, and ATCC25922. As shown in Figure 5, at a concentration of $5 \times 10^5$ CFU/mL, all three nonspecific cells showed only background signals, all at much lower intensities than the specific O157:H7 cells. The background from DH5α and ATCC25922 cells was negligible. We also tested different concentrations of all three nonspecific cells, from $5 \times 10^3$ to $5 \times 10^6$ CFU/mL, and they all had signal intensities similar to the blank.

We noted that the signal intensities increased with the increase of *E. coli* cell concentrations in the sample, as expected, but these increases were not completely linear over the large concentration range (Figure 4). We suspected that the nonlinearity observed at the high bacterial concentrations could be due to cell aggregation, reducing the cell surface area for binding to the antibody. Because we had on average five antibody molecules attached to each Au NP, these Au NPs could bring bacterial cells together. Aggregation of the cells would decrease their surface area available for binding to the antibody-conjugated Au NPs, which would result in signals lower than expected for high concentrations of cells. In order to test this hypothesis, we measured the average number of Au NPs bound to each CFU after we incubated a fixed amount of Au NPs with increasing concentrations of bacterial cells (Figure 6). We found that as the cell concentration increased from $5 \times 10^2$ to $5 \times 10^6$ CFU/mL, the amount of Au NPs bound to each CFU decreased from $1.1 \times 10^6$ to $7.8 \times 10^3$. These results support our hypothesis and suggest that the assay is more useful for detecting low concentrations of the target cells. Decreasing the loading of antibodies on Au NPs and increasing the concentration of Au NPs may improve linearity for the high bacterial concentration range; however, aggregation of Au NPs could potentially be an issue. Another possible reason for the nonlinearity at very high concentrations of bacterial cells could be due to the insufficient amounts of antibody needed to bind with excess sites on the bacterial cells.

We also explored the use of commercially available biotinylated polyclonal antibody and streptavidin-coated Au NPs, in an attempt to broaden the application of the assay. Because of the strong

binding between biotin and streptavidin, streptavidin-coated Au NPs could be used with a range of biotinylated antibodies for other targets. Our preliminary results from the use of biotinylated polyclonal antibody to all *E. coli* O and K strains showed lower specificity and binding ability to *E. coli* O157:H7 compared to the use of directly modified Au NPs with monoclonal antibody. Nonetheless, a dynamic range from $5 \times 10^4$ to $5 \times 10^7$ CFU/mL was achieved with a detection limit of $5 \times 10^4$ CFU/mL (Figure S1 in the Supporting Information).

In conclusion, we have demonstrated a sensitive, specific, and rapid assay for *E. coli* O157:H7 based on the combination of monoclonal antibody recognition, gold nanoparticle labeling, and inductively coupled plasma mass spectrometry detection. The assay was able to detect bacterial cells in a large concentration range and with a detection limit comparable to most immunoassays or sensor-based assays. Commonly used sample preconcentration techniques (e.g., the use of antibody-coated magnetic beads or immuno membrane filtration) could further improve the detection limit of the assay. In addition to Au NPs, other nanoparticles (e.g., silver nanoparticles and rare earth nanoparticles) could also be used as specific labels. Because ICPMS is capable of specific detection of multiple elements, high-throughput analyses of multiple bacterial cells could be achieved by labeling antibodies for different cells with different nanoparticles. The feasibility demonstrated here for the analysis of *E. coli* O157:H7 suggests the potential of similar immunoassays for a wide variety of bacterial pathogens.

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## SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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