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Single Gold Microshell Tailored to Sensitive Surface Enhanced Raman Scattering Probe

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We finely tuned the Au shell on a polystyrene microsphere of 2 μm in diameter to achieve a strong surface enhanced raman scattering (SERS)-active platform so that the molecules on a single microspherical shell surface produce their own fingerprint SERS spectra. The proposed microshells can be easily and individually manipulated under a conventional optical microscope using a micropipet and act as a sensitive probe to obtain the SERS spectra of the monolayer of molecules on Pt as well as Au surfaces without any requirement of special surface morphology or modification for inducing SERS activity. Well-defined SERS spectra can be obtained at a very short acquisition time of milliseconds, suggesting useful applications of the present system based on the decoding of the SERS-active barcodes on individually functionalized microshells.

Surface enhanced raman scattering (SERS) has been a subject of intensive research since it suggests many useful applications such as biological sensing and trace analysis.[1] The unique signal enhancement of SERS reportedly allows the detection of analytes even at the single-molecule level. It is widely accepted that the large signal amplification in the SERS process arises from the electromagnetic enhancement at so-called "hot spots", which may be either interstitial sites or the surface of nanosized materials. Moskovits et al. proposed a simple strategy to create the hot spots by introducing closely spaced nanowires and showed that the enhancement is a function of interstitial distances.[2] They also demonstrated a chemically patterned SERS-active system where the hot spots are easily found and analyzed.[3]

Electrochemically roughened metal surfaces and colloidal nanoparticles were traditionally employed as SERS substrates.[1] Recently, more stable and controllable SERS-active substrates were reported including nanoparticle arrays fabricated with nanosphere lithography,[4] nanowire bundles,[2] and metal surfaces by templated electrodeposition.[5] On the other hand, tip-enhanced Raman scattering (TERS) has received extensive attention since it can provide a high spatial resolution as well as specific chemical information.[6] However, TERS at the present stage requires highly sophisticated setups and suffers from low signal enhancement, poor reproducibility, and difficulty in working in aqueous media. It was also reported that a tapered optical fiber coated with silver islands can be utilized as a nanoprobe inducing SERS signals from chemicals on any type of surfaces.[7]

Halas et al. proposed a somewhat different approach, where a nanoshell geometry consisting of a dielectric core with a thin gold coating is utilized as SERS-active substrates.[8] The individual nanoshell as a SERS probe may offer an efficient method to identify the molecules on a SERS-inactive substrate, which has been one of the challenging issues in current surface analysis. In spite of the attractive features of this strategy, the nanoshells have critical drawbacks for the purpose of surface identification. Since they are invisible by a conventional optical microscope, it is difficult to place them on the spot of our interest and also to ensure where they are present. This prohibits potential applications of nanoshells, e.g., an in situ biological SERS study such as cell membrane imaging. In addition, individual nanoshells are too small to be manipulated and, thus, hardly removed from the surface after SERS measurements. When it comes to cell surface imaging, not only nanoshells but also other materials on the similar scale like nanoparticles, nanorods, nanotubes, and nanowires are potentially toxic contaminants to the living cells or tissues because they could be engulfed by the cells through endocytosis.[9−13] The capability of individual manipulation and thereby effective removal of SERS-active substrates is essential for in situ surface imaging.

Another promising application of an individual SERS-active particle to modern bioanalysis is the multiplex assay, which is

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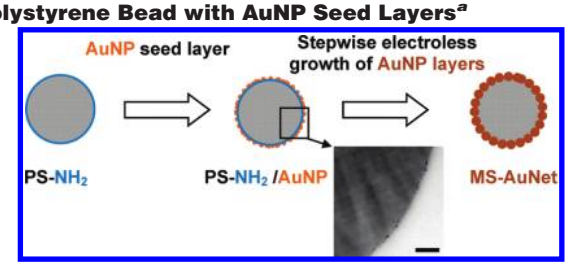
based on the respectively barcoded microbeads in combination with a couple of the SERS tags flowing in microfluidic channels.[14,15] This strategy, which is called "micro suspension array", increasingly attracts keen attention to simultaneously acquire more information in a smaller volume of sample within a shorter period.[16] However, the conventional polymer or silica beads of several hundred micrometers in diameter are required to be improved in terms of size and material for the suspension array operating on microfluidic chips. Smaller beads could allow smaller sample volume and higher throughput screening with sufficiently sensitive and reliable decoding techniques. Although the small bead systems such as nanoshells possess many attractive properties for this purpose, there are still serious limitations. The nanoshells are too small to be recognized and individually manipulated by a conventional optical microscopy. Moreover, the SERS signals from a single nanoshell are too weak to be identified for a short exposure time, during which the decoding process should be completed.

Here, we propose a polystyrene microsphere with a finely tuned SERS-active Au network structure (MS−AuNet) from which SERS signals are maximized. There have been a few reports on the fabrication of silver-coated microsphere systems that can be used as SERS-active substrates.[17−19] The MS−AuNet suggested in the present work is larger than the conventional nanoparticles or nanoshells that have been reported as SERS-active materials, while it has the smallest dimension that can be routinely recognized by a conventional optical microscope. Particles smaller than MS−AuNet suffer from weak SERS signals and difficulty in optical recognition and manipulation. Larger particles than MS−AuNet are less efficient in terms of resolution for surface probing as well as sample volume for fast multiplex analysis. The diameter of the MS−AuNets is largely comparable with that of the focal area of focused laser that are normally used for SERS measurements. When a laser beam is focused on a MS−AuNet, SERS signals are not expected to arise from a part of its surface but from almost the entire one. MS−AuNets have thin Au layers through which laser beam can penetrate, and thus, SERS-based surface probing is enabled by just being placed on the spot of interest and focused by a laser. The polymeric inner cores offer the opportunities to adjust the specific gravity and to make the MS−AuNets magnetic if necessary. On the basis of these characteristics of micrometer-sized polymer/Au core/shell systems, MS−AuNet in the present study suggests practical applications to not only sensitive surface chemical probing but also high throughput SERS-based decoding of barcoded microbeads.

EXPERIMENTAL SECTION

Preparation of MS−AuNets. Colloidal gold nanoparticles (AuNPs, 2 to 3 nm in diameter) were synthesized by the procedure in the literature[20] and attached to amine-terminated polystyrene beads (PS−NH_2) as seed layers (Supporting Information A).[21] Scheme 1 shows a brief procedure of MS−AuNets preparation including a typical cross-sectional transmission electron microscopy (TEM) image of a polystyrene bead with AuNP seed layers. Each electroless plating step was conducted as follows.[22] A 20 mL aliquot of the Au plating solution (Supporting Information A) and 140 μL of 37% formaldehyde were added to 1 mL of PS−NH_2/AuNP solution. The mixture was stirred vigorously, and a dark blue-colored suspension was obtained within 2 min. This solution was centrifuged at 2000 rpm for 5 min, and the supernatant was decanted. After adding 20 mL of water, the solution was centrifuged at 2000 rpm for 5 min and the supernatant was decanted. This electroless plating process was repeated 1, 5, 10, 20, and 30 times for preparing different surface topology of MS−AuNets.

Scheme 1. Procedure of Stepwise Electroless Plating on a Microbead and Cross Sectional TEM Image of a Polystyrene Bead with AuNP Seed Layers[a]



[a] Scale bar = 100 nm.

Instruments. SERS spectra were obtained using a homemade Ramboss Micro-Raman system spectrometer with a 632.8 nm line from a 20 mW He/Ne laser (Model LGK7665) as the excitation source. For TEM measurements, the MS−AuNets were mixed with embedding media and were polymerized. The samples were then sliced to 80 nm by an ultrasection and TEM images were obtained using an Energy-Filtering Transmission Electron Microscope (LIBRA 120, Carl Zeiss, Germany). Micropipets for trapping a MS−AuNet were fabricated by heating and pulling borosilicate glass capillaries in a laser-based micropipet puller device (Sutter Instruments Inc., P-2000).

RESULTS AND DISCUSSION

Optimal SERS Activity of MS−AuNets. Figure 1a shows the SERS spectra obtained from a solution containing PS−NH_2/AuNPs or MS−AuNets dispersed in ethanol with 1 mM 4-nitrobenzenethiol (NBT) as a function of the number of electroless plating steps. No SERS intensity was observed from the polystyrene beads covered with AuNPs (PS−NH_2/AuNP), and all the peaks in the spectrum originated from ethanol solvents. As the Au layer is plated, the SERS peaks from NBT adsorbed on MS−AuNPs appear as indicated by arrows in Figure 1a. The peak positions are in good agreement with those obtained from a NBT solution. (See the Supporting Information B for peak assignments.) The enhancement of the SERS signals sensitively varies with the number of plating steps among which

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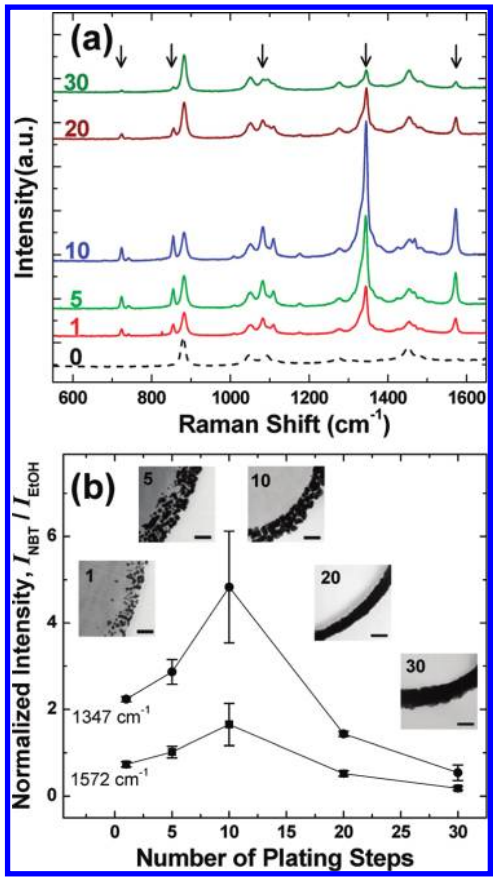

Figure 1. (a) SERS spectra obtained from a solution containing PS−NH_2/AuNPs or MS−AuNets dispersed in ethanol with 1 mM NBT as a function of the number of electroless plating steps (specified on the left side). The SERS peaks from NBT adsorbed are denoted with arrows. (b) Normalized SERS intensities as a function of the number of Au plating steps. Insets show cross-sectional TEM images of MS−AuNets with different numbers of plating steps (bar: 100 nm).

10 times of plating steps produce the maximum intensity. More than 10 times of plating steps result in a rapid decrease of the SERS intensity, and the peaks from NBT almost disappear upon 30 times of plating steps. The intensities of the 1347 cm^{-1} and 1572 cm^{-1} bands from NBT were normalized with respect to a characteristic band from ethanol (883 cm^{-1}) and plotted as a function of the number of plating steps as shown in Figure 1b.

Figure 1b also shows the cross-sectional TEM images of MS−AuNets, which rationalize the dependence of SERS activity on the number of plating steps. The AuNPs of the seed layer on a polystyrene bead (TEM image is shown in Scheme 1) create no effective hot spots. A similar result was previously reported that SERS activities from individual AuNPs fixed on a flat silicon wafer surface were negligible until the interparticle coupling became remarkable at sufficiently small interparticle distances.[23] In the present study, the first Au plating step makes the AuNPs grow to larger particles with an average size of ca. 20 nm and some of which coalesce with each other. The increasing SERS activity indicates that the hot spots[24] begin to emerge. Further, Au plating steps lead the Au particles to densely interconnected Au networks. The SERS activity reaches the maximum when such

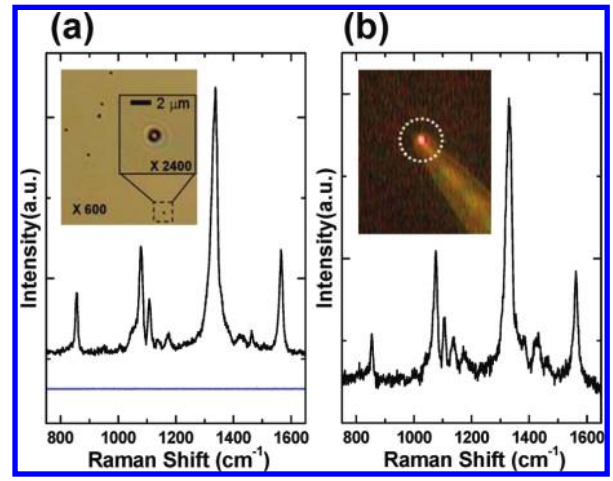

Figure 2. (a) SERS spectrum from a single MS−AuNet modified with NBT (shown in a box) on which the laser is focused (black line). Blue line was the SERS spectrum obtained with the laser focused on a bare glass surface. Acquisition time was 1 s. Inset shows an optical microscopic image of MS−AuNets placed on a slide glass. (b) SERS spectra from a single NBT-modified MS−AuNet trapped at the end of a micropipet tip. The conditions for measurement were the same as those in (a). Inset shows the optical microscopic image of a MS−AuNet trapped by a micropipet.

porous Au nanonetworks appear on the surface of the microspheres, indicating the presence of abundant hot spots. On the other hand, excess plating more than 20 times, repetitively, makes the SERS activity almost disappear. As the Au nanonetwork becomes smooth, MS−AuNets rapidly lose the SERS activity. This behavior is quite different from that observed on the nanoshell structures, where the SERS activity is maximized when Au shell layers are nearly completed.[8] The SERS activity of the nanoshells arises mainly from the interacting plasmon due to the shell geometry of the completed Au shells.[25] The SERS activity of the microspheres in the present study originates from incomplete network structures on the microspherical surface.

Such an optimal SERS intensity is observed not only in ethanol but also in water (Supporting Information C). MS−AuNets suffer from no serious self-aggregation unlike nanoparticles or nanoshells. In addition, the adsorbates on MS−AuNets are safely intact throughout a series of processes. After two kinds of MS−AuNets respectively modified with two different Raman tags of 4-aminobenzenethiol (ABT) and benzenethiol (BT) are mixed in pure water and stored for several hours, the SERS spectra from those two kinds of MS−AuNets show no contamination to each other (Supporting Information D). This is an important aspect for thiol-modified particles for analytical applications. Considering that AuNPs require stabilizers and suffer from instability, MS−AuNets provide many valuable advantages, and this would be more evident for analyses on microfluidic chips.

SERS from a Single MS−AuNet. NBT-modified MS−AuNets sprinkled on a glass slide are easily recognized through a conventional optical microscope (Figure 2a, inset), and a laser beam could be focused on the center of a single MS−AuNet to obtain SERS spectra as shown in Figure 2a. SERS signals from a single MS−AuNet are strong enough to produce well-defined

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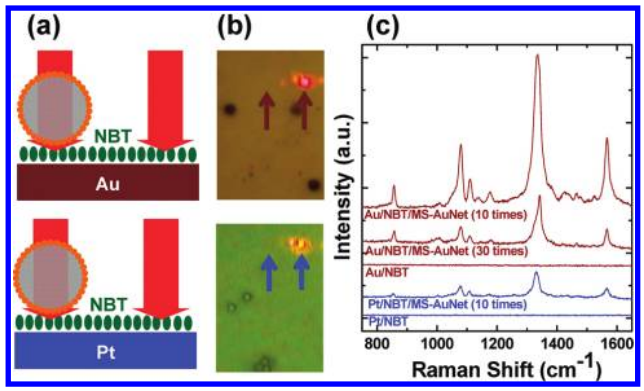

Figure 3. SERS induced by a single bare MS−AuNet. (a) Schematics for SERS-induced interfaces. (b) Optical images of MS−AuNets on Au or Pt substrates. Laser probe is indicated by arrows. (c) SERS spectra from a NBT monolayer on Au (green lines) and Pt (blue lines) substrates. Acquisition time was 1 s.

spectra even for 1 ms of acquisition time (Supporting Information E). Randomly sampled 100 NBT-modified MS−AuNets give well-defined SERS spectra. Several consecutive measurements with a NBT-modified MS−AuNet result in no significant deterioration in the SERS spectra, which unequivocally tells the reliable and sustainable SERS activity of the MS−AuNets. We can also individually handle a single MS−AuNet using a micropipet. Just sucking through a micropipet makes a single MS−AuNet trapped at the end of a micropipet tip. Figure 2b shows a SERS spectrum obtained from a single NBT-modified MS−AuNet trapped in such a way. There is no noticeable difference between SERS spectra from trapped and free single NBT-modified MS−AuNets. This indicates that a single MS−AuNet could be carried to any place of our interest where the corresponding SERS spectrum should be obtained. A MS−AuNet is small enough to be dipped into a subpicoliter solution and, thus, expected to possibly give SERS spectra corresponding to the analytes in such a small sample volume.

Considering the focal area of the laser beam, the size of a single MS−AuNet corresponds to the largest scale of the spherical SERS-active substrate that generates from its entire surface. Larger beads than MS−AuNets produce SERS signals from only a part of the surfaces. On the other hand, MS−AuNets are the smallest beads that can be individually handled by currently available manipulating tools under a conventional optical microscope, as will be shown in another section. In these respects, SERS spectra from a single MS−AuNet suggest a new approach to chemical identification of surfaces and combinatorial micro suspension arrays. In addition, the maximized SERS sensitivity and stability on individual MS−AuNets allow combinatorial SERS-based decoding by immobilizing multiple Raman tags (Supporting Information F).

Surface Probing by a MS−AuNet. A bare single MS−AuNet placed on a monolayer of NBT on Au substrates induces a SERS-active environment. Figure 3a shows schematics for SERS activity induced by a single unmodified MS−AuNet on NBT self assembled monolayers (SAMs) on Au or Pt surfaces. Each MS−AuNet placed on NBT monolayers was focused by laser probes (Figure 3b), and the resulting SERS spectra are shown in Figure 3c. The 10-times plated bare MS−AuNet provides not only hot spots on its own surface but also a nanogap effect through interactions with metal layers. Recently, SERS activity from nanogap effect between metal surfaces and AuNPs or Au nanowires was reported.[26,27] Figure 3c also shows that MS−AuNet with 10-times plating produces significantly larger signals than those from a 30-times plated MS−AuNet that has a complete layer of Au shell. The SERS activity due to a 30-times plated MS−AuNet originates from only the nanogap effect, since the complete Au shell layer on microsphere exhibits negligible SERS activity by itself. SERS enhancement factors (EFs) of the 10-times plated MS−AuNets placed on a Au surface are calculated to be around 5×10^3 (Supporting Information G). Here, the A_{SERS}, the area that produces the SERS signals, is assumed to be the area where the distance between the surface of MS−AuNet and Au substrate is less than 10 nm, which is a critical distance for inducing SERS activity based on the nanogap effect.[24] This EF value is comparable to those for other metal−metal junction systems that were previously reported.[26,27]

Importantly, a single bare MS−AuNet can be also utilized to obtain SERS spectra of chemical species on Pt as well as Au. The SERS signals from a bare MS−AuNet on a monolayer of NBT on a Pt surface is smaller than those on Au surfaces. In this case, the EF is calculated to be 6×10^2. It is well-known that Pt exhibits weaker SERS activities than Au and nanostructured Pt surfaces have SERS EFs in the order of 10^3 or smaller.[28,29] The SERS spectra induced by MS−AuNets on Pt surfaces are strong and reproducible enough to chemically identify the organic monolayer on a Pt surface. Furthermore, it should be noted that the proposed system requires neither special morphology nor chemical modification of the Pt surfaces on which an organic monolayer lies.

A bare single MS−AuNet can be displaced using a micropipet and maintain the capability of a SERS-active substrate as shown in the preceding section. Exploiting this feature, we conducted chemical identification of the multiple sites on a given surface with one bare MS−AuNet, which is carried by a micropipet linked to a manipulator as shown in an optical image in Figure 4. Figure 4 illustrates the scheme of multiple surface identifications based on the proposed carriable SERS probe and the corresponding SERS spectra. SERS spectra from one bare MS−AuNet successfully represent ABT and NBT monolayers that are on different places. When a bare MS−AuNet was trapped at the end of a micropipet tip and pulled out of the surface, no SERS signal was obtained. This indicates that the MS−AuNet is not contaminated by thiols on the substrate (Supporting Information H). The processes of trap, translocation, and surface probing by SERS measurement can be performed reproducibly with an individual MS−AuNet.

CONCLUSIONS

We sophisticatedly optimized the Au surface on a 2 μm polymer microsphere to achieve a strong SERS-active platform so that the molecules on the surface of a single MS−AuNet produce their own fingerprint SERS spectra. The proposed MS−AuNets can be easily identified and individually addressed using a conventional

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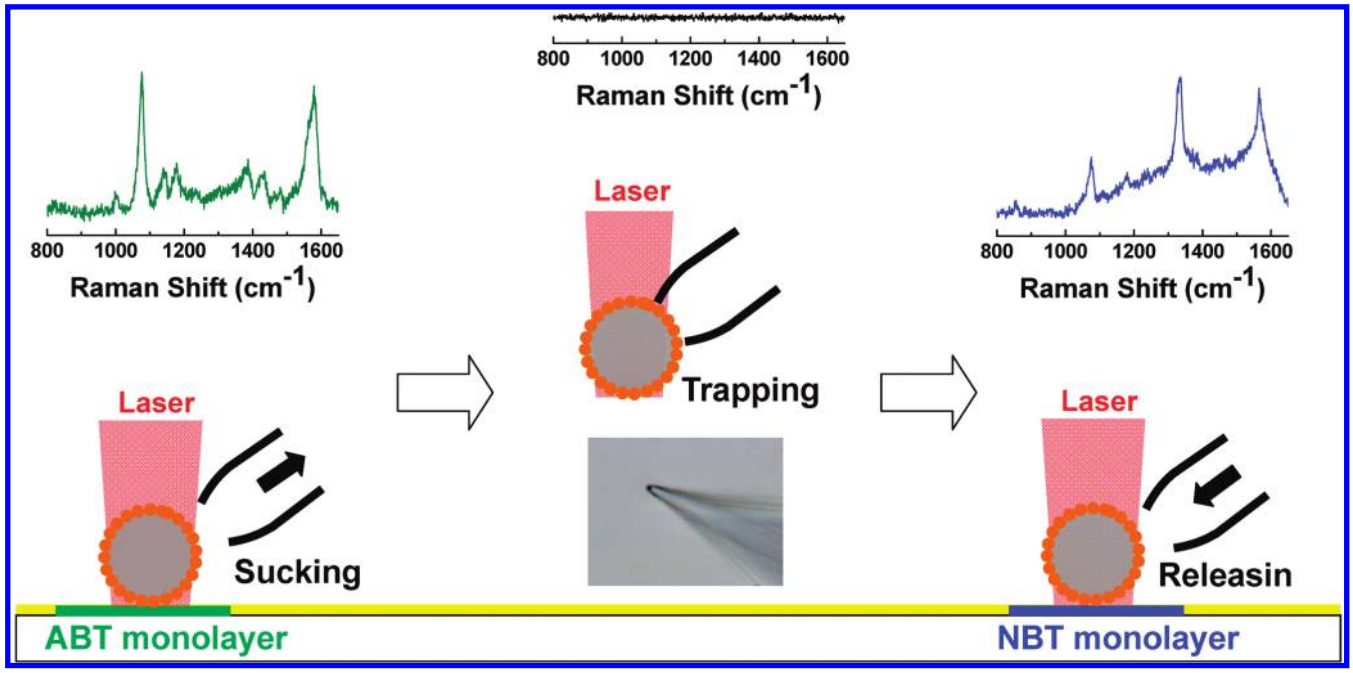

Figure 4. Scheme of transferring and placing a MS−AuNet on the spots of interest. SERS spectra were obtained from a bare MS−AuNet placed on the ABT layers (green), trapped at the tip end of a micropipet (black), and released on NBT monolayers on another spot (blue). Both organic monolayers are on Au substrates, and the SERS spectra are from one MS−AuNet carried by a micropipet. The acquisition time was 1 s. An optical microscope image shows a MS−AuNet trapped at the tip end of a micropipet.

optical microscope. A single MS−AuNet possesses physical properties suitable for a probe to obtain Raman spectra of monolayered molecules on Au and Pt surfaces. The SERS signals from a single MS−AuNet are so strong that only 1 ms of acquisition time is enough to achieve well-defined spectra. These results imply high throughput decoding the microbeads with multiple Raman tags in a microfluidic system. Using a typical micropipet as shown in this study or possibly optical tweezers, a single MS−AuNet could be precisely placed on the surface of our interest, translocated to another spot, and finally removed from the surface under the naked eye with monitoring through an optical microscope. Since the SERS activity of a MS−AuNet is stably sustained in water, this system can be utilized for in situ surface chemical probing in aqueous phases, which is crucial for SERS imaging of biological membranes and studying electrocatalytic mechanisms. The MS−AuNet in this work offers new opportunities for SERS-based probing techniques to a wide range of valuable applications such as a reliable and practical way of nondestructive spectroscopic identification of chemically modified surfaces, in vivo chemical or biological monitoring on the membrane of a living cell like a neuron or stem cell, and high throughput decoding of microbead suspension arrays in microfluidic systems.

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SUPPORTING INFORMATION AVAILABLE

The experimental details and additional SERS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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