J. Microbiol. Biotechnol. (2007), **17**(1), 5–14

JOURNAL OF MICROBIOLOGY AND BIOTECHNOLOGY

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Nanotechnology in Biodevices

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Received: October 30, 2006
Accepted: November 29, 2006

Abstract Nanotechnology is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer. The technology has been applied to biodevices such as bioelectronics and biochips to improve their performances. Nanoparticles, such as gold (Au) nanoparticles, are the most widely used of the various other nanotechnologies for manipulation at the nanoscale as well as nanobiosensors. The immobilization of biomolecules is playing an increasingly important role in the development of biodevices with high performance. Nanopatterning technology, which is able to increase the density of chip arrays, offers several advantages, including cost lowering, simultaneous multicomponent detection, and the efficiency increase of biochemical reactions. A microfluidic system incorporated with control of nanoliter of fluids is also one of the main applications of nanotechnologies. This can be widely utilized in the various fields because it can reduce detection time due to tiny amounts of fluids, increase signal-to-noise ratio by nanoparticles in channel, and detect multi-targets simultaneously in one chamber. This article reviews nanotechnologies such as the application of nanoparticles for the detection of biomolecules, the immobilization of biomolecules at nanoscale, nanopatterning technologies, and the microfluidic system for molecular diagnosis.

Key words: Nanotechnology, biodevice, nanoparticle, nanopattern, nanoelectromechanical systems

The nanotechnologies have been rapidly developed for past decades in order to utilize new properties of materials by the miniaturization of a volume of considering materials such as gold (Au), ever since Feynman [25] had lectured about the tremendous possibilities of nanotechnologies at California Institute of Technology in 1959. Currently, nanotechnologies include control technologies of nanoliter (1 billionth of a liter) amounts of fluids as well as control of matter on the nanometer (1 billionth of a meter) length scale.

Miniaturization of a system such as materials, devices, and systems has various advantages as well as acquirement of new properties of materials; 1) tremendous increment of surface capability due to enlarged surface-volume ratio, 2) shortened transport time of molecules by short distance, 3) high linear flow rate acquirement with tiny sample loading system, 4) almost limitless expansion of detection spot in the case of arrays, etc. Surface effects (such as biofouling) by the increased possibility of collision between molecules and a surface in the microreactors due to high surface-volume ratio may not be ignored, whereas there are many merits from miniaturization such as increased reaction rate in a nanoliter scale reactor.

Various types of nanotechnologies have been direct-incorporated to biodevices for enhancement of the signal-to-noise ratio and the reduction of time to answer out of bioanalytical system in the fields of clinical diagnosis, as well as in drug delivery systems and clinical medicine. In particular, nanoparticles, nanowires, and nanopatterning technologies have been applied widely to biodevices such as nanoarrays, nanobiosensors, and microanalytical systems (Lab on a chip). The nanotechnologies applied to biodevices can be categorized into four potential fields: 1) nanoparticles technologies such as Au particles [13], magnetic nanoparticles that can be combined with MRI [40], and quantum dot [43]; 2) nanosensors technologies including the single nanopore sensor to detect single nucleic acid molecule [21], PEBBLE (probes encapsulated by biologically localized embedding) sensor [11], SPR (surface plasmon resonance) sensor [57], nanomechanical sensor using nano cantilever, and bioFET utilizing silicon or carbon tube nanowires as a gate [27], and nanoelectrode electrochemical sensor [49]; 3) nanoarray technologies by nano contact imprinting

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technologies [9] and dip-pen technology [41]; and 4) microfluidic system incorporated with control of nanoliters of fluids such as the micro pump/valve system [7], surface modification technologies [51], and NEMS (nanoelectromicro system, referred to as MEMS) [2]. Biodevices applying such nanotechnologies mentioned above can detect biomolecules in the femtomole concentration by enhancement of signal amplification [4], and diagnose/treat a cancer [69], and are used in drug discovery [23]. Lab on a chip technology is one of the main applications of nanotechnologies [17]. This can be widely utilized in various fields, for example, POC (point of care), drug discovery, U-health system, and environmental monitoring, because it can reduce detection time due to tiny amounts of fluids, increase signal-to-noise ratio by nanoparticles in channel, and detect multi-targets simultaneously in one chamber.

This paper reviews in detail about nanoparticles application, particularly Au nanoparticles for the detection of biomolecules, biomolecules immobilization at the nanoscale, nanopatterning technologies that are able to increase the density of chip arrays, and microfluidic system for molecular diagnosis.

NANOTECHNOLOGIES IN BIODEVICES

Nanoparticle Applications

Recently, many advances were achieved in the electrochemical and optical detection of DNA and immuno-reactions, through the use of innovative detection schemes and new materials, particularly the use of nanoparticles. This advanced technology has been extended throughout the field of biosensors and biochips. Specifically, nanoparticles (including nanotubes and nanowires) made from metals, semiconductor, carbon, or polymeric materials have been widely investigated to enhance the reaction signal of bioreceptors such as enzymes, antibodies, and oligonucleotides [55].

Nanoparticle application in electrochemical biosensors, especially DNA biosensors, has been studied [33]. The electrochemistry is improved by the reduction of the distance between the redox site of a protein and the electrode using the small nanoparticles. The application of carbon nanotubes (CNTs) in biosensors has been reviewed recently [65], and the use of magnetic nanoparticles has also been reported [34]. Metal nanoparticles, in particular Au nanoparticles, can be used for the improvement of performance of biosensing [31]. They have been used as the fluorescence quenchers to develop an optical biosensor and as the biochemical catalyst. They can also be used to enhance the amount of biomolecules immobilization on a sensor electrode surface.

SPR technology has been spotlighted as an alternative of detection methods in biological sensing device owing to its ability of label-free detection. In particular, signal transduction is difficult or impossible to accomplish, and this detection technique is superior to conventional response detection techniques. High resolution also makes this technique more powerful. SPR has been used to measure biomolecular binding on solid surfaces such as thin-film fabrication, DNA hybridization, antibody-antigen recognition, epitope mapping, and protein arrays [35].

However, the use of the SPR method is hindered, and it shows a limited sensitivity when the change of the refractive index as a result of binding event is little, which might be caused by the binding of small molecular weight materials. This drawback can be overcome through an adequate label, which guarantees reliable and specific binding capacity to the target. Metal or magnetic nanoparticle-based analytical technique can fulfill these requirements. Several researchers have reported that the nanoparticle-based label could be successfully applied for immunochromatography, conductance measurement, surface enhanced-raman scattering, etc. [45].

Au nanoparticles have been known to provoke an outstanding angle shift in plasmon resonance, and therefore, Au nanoparticle-antibody conjugates were used for the signal enhancement of SPR for immunosensing [62]. A significant enhanced change in SPR curves (~25-fold) compared with that observed in the absence of Au nanoparticle was reported. In addition, several researchers have reported that the Au nanoparticle-antibody conjugate can be used for the enhancement of the SPR curve; however, their works were not enough for determining linear relationships, particularly in the low detection range. Their results showed non-negligible deviations in calibration curves, due possibly to the random orientation of antibody attached on the Au nanoparticles. Many researchers published articles with respect to the fabrication of the Au nanoparticle-DNA conjugate and Au nanoparticle-antibody conjugate. An antibody fragment, which has a strong binding affinity region in the entire molecule, can be a clue to the development of reliable and accurate biosensing devices in a wide range of applications such as clinical diagnostics and the monitoring of diseases. Using the orientation-controlled immobilization of antibody fragments, a metal-protein hybridized surface can be fabricated with regular size distribution, and it can enhance the limit of detection in the biological sensor system.

We reported that an Au nanoparticle-antibody complex could be fabricated by using the antibody fragment and applied to the amplification of the SPR signal [45]. In that study, application of an Au nanoparticle-antibody complex was carried out for signal enhancement of an SPR sensor. A biomolecular thin film was fabricated with the antibody fragment and the proposed system could improve the limit of detection compared with the label-free SPR analytical devices. The schematic diagram of the proposed immunoassay

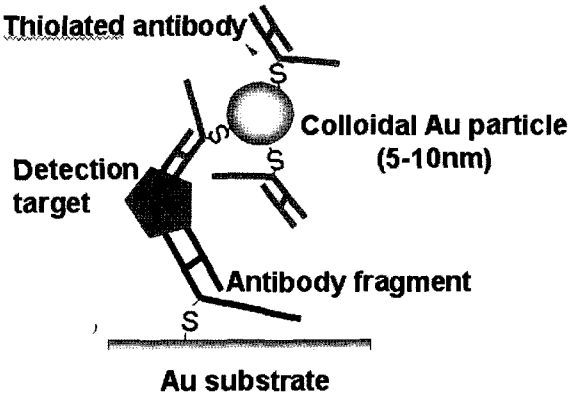

Fig. 1. Schematic configuration of immunoassay using the conjugate of Au nanoparticle and antibody fragment.

system is shown in Fig. 1. Experimental results demonstrated that the proposed immunoassay system was compatible with the postulated specific antibody-antigen binding mechanism. Furthermore, many Au nanoparticle complexes specific to a variety of target molecules can be fabricated on the basis of unique chemistry with the derived optimal condition. In particular, the proposed assay using a Au nanoparticle-antibody complex can be a versatile technique for the detection of low molecular weight target materials that are difficult to measure by using conventional SPR sensors. For the detection of human serum albumin (HSA), the proposed Au nanoparticle complex showed 10^4-fold signal enhancement in parallel with femto-level detection.

An Au nanoparticle-antibody complex was applied to a scanning tunneling microscopy (STM)-based electrical system for detection of protein [18]. A schematic of the detection system is shown in Fig. 2. The detection method is based on the change of tunneling current at Au nanoparticles dispersed on the surface of Au substrate insulated with organic/bio material.

As proof-of-concept for the electrical detection method of proteins by STM, we evaluated its performance with prostate-specific antigen (PSA). In a typical experiment, anti-PSA fragments were immobilized on the surface of the Au substrate, where the anti-PSA fragment was prepared for the improved immobilization based on an Au-thiol

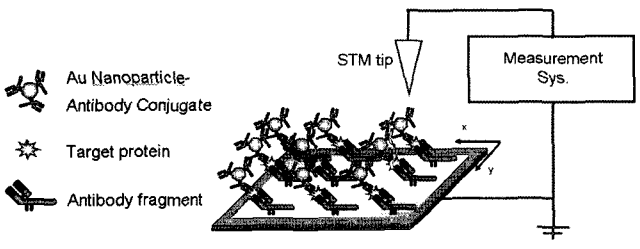

Fig. 2. Schematic diagram of scanning tunneling microscopy-based electrical system for detection of protein.

interaction. The anti-PSA immobilized Au substrate was added to a solution containing PSA. After the substrate had been given a chance to react with PSA, the Au nanoparticle surface-functionalized with anti-PSA fragments were added to form a sandwich structure with anti-PSA fragments on the Au surface that has captured target. After washing, the electrical response by the positional distribution of Au nanoparticle formed with the sandwich structure on the substrate was investigated using current scan mode of STM. As a result, the frequency of current peaks was generated in accordance with the surface density of the dispersed Au nanoparticles on the surface, which was represented as a periodogram with its logarithmic regression curve. The change of the power spectrum was observed in accordance with the concentration of PSA molecule. The lowest detection limit of the assay system for PSA is ~fg/ml. It exhibits a sensitivity that is four orders of magnitude more sensitive than conventional ELISA detection methods for PSA.

Thin-Film Preparation Technology

Recently, thin-film preparation technology has played an important role in the high technology industries. One of the well-known techniques in thin-film preparation techniques is the conventional vacuum evaporation, due to its simplicity and convenience. Although well-established techniques such as conventional vacuum evaporation, sputtering, and chemical deposition are able to make good results, the increase in the range of thin-film applications has led to the development of various deposition techniques including electron beam evaporation, molecular beam epitaxy (MBE), metal organic chemical vapor deposition (MOCVD), and plasma CVD.

These techniques, however, have a drawback of covering only inorganic materials. There are some prerequisites for the deposition of organic and/or biological molecules. During the deposition process, deposited molecules should not be degraded and the orientation of deposited molecules should be maintained by a given technique. Compared with the inorganic materials, most organic or biological molecules are easily degraded by some changes in their environments, and their functionality, which is affected by the molecular orientation, is mainly driven from the specific molecular interactions with the neighboring molecules. In principle, however, it is not possible to satisfy those prerequisites by using the conventional chemical or physical deposition techniques, such as CVD, vacuum evaporation, and sputtering. Without a loss of the specific functionality, high-quality and ordered monolayers or multilayers of organic or biological molecules onto substrates can be built up using the Langmuir-Blodgett (LB) and self-assembly (SA) techniques [14, 24].

In these techniques (LB and SA), the types of surfaces to which biomolecules such as proteins can be immobilized

fall into two categories. The first and simplest type of immobilization is physical adsorption onto surfaces by Van der Waals, hydrophobic, and hydrogen-bonding interactions. The advantage of this type of immobilization is that it is very simple to perform because it does not require any modification of the biomolecule. The disadvantage is that most of the immobilized biomolecule can be inactivated owing to denaturation and steric occlusion [12]. A preferred method relies on one or a small number of strong bonds between the biomolecule and surface, leaving the biomolecule largely unaltered, except in the vicinity of the contact point. For example, it would include the covalent attachment of biomolecule, immobilization of biotinylated biomolecules onto a streptavidin-coated surface, and immobilization of His-tagged biomolecules onto a Ni^{2+}-chelating surface [3, 61, 70]. However, owing to this common method for immobilizing biomolecules through (or biotin-based) interactions by randomly conjugating lysine residues on biomolecules to amine-reactive surfaces (or biotinylation reagents), in order to construct the biodevice with high performance, the immobilization techniques of biomolecules needs to be develop in an oriented fashion [15, 16, 58, 64, 66].

We reported the thin-film preparation of biomolecules by the LB technique and SA technique in an oriented fashion, and its applications to a bioelectroluminescent device (bio-EL) and SPR immunosensor, respectively [38, 59].

In the former, a bio-EL device was fabricated by the application of photo-excited characteristics in chlorophyll *a*. The bilayered bio-EL device composed of ITO/viologen/chlorophyll *a*/Al was fabricated by using an LB technique, and the schematic configuration and energy diagram are shown in Fig. 3. In the study, we investigated the EL properties of bio-EL devices at various thicknesses of chlorophyll *a* LB layers (25 layers and 15 layers) and external quantum efficiency of bio-EL, and the luminescence of the bio-EL device. The fabrication of a multilayer as well as the control of molecule orientation is one of the

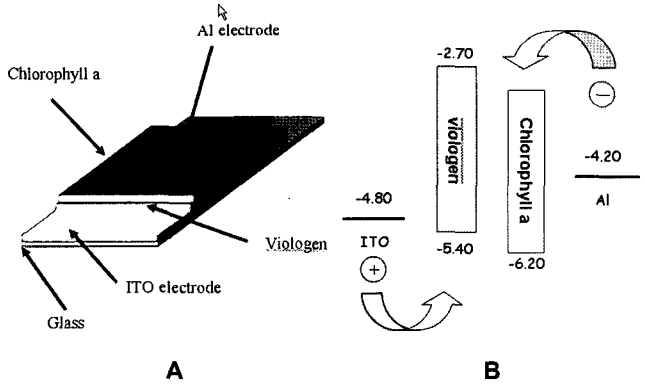

Fig. 3. Schematic configuration (**A**) and energy diagram (**B**) of the bilayered bio-EL device.

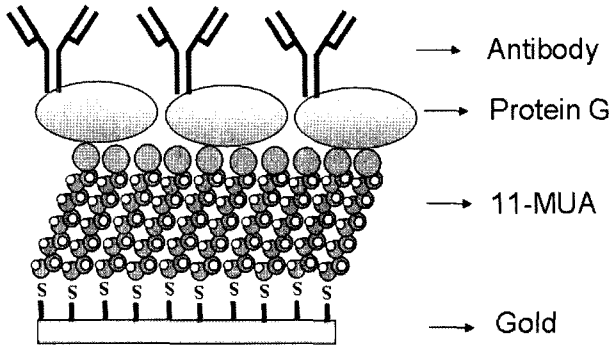

Fig. 4. Schematic diagram of the antibody immobilization via protein G on a solid surface by the SA technique.

advantages of the LB technique. The constructed bio-EL device, using viologen as the hole-transporting layer [which is valuable as the hole-transporting material because the HOMO level is located between ITO and chlorophyll *a* (Fig. 3B)], exhibited the narrow blue emission peak around 455 nm, and this device showed the high external quantum efficiency of 1.0×10^{-3}% in the range of 17 V and the low turn-on voltage of 5 V.

In the latter, we developed an immunosensor based on SPR using protein G for the detection of *Salmonella typhimurium*. The protein G, a cell wall protein found in most species of *Streptococci*, was used as the binding material in order to construct a well-defined antibody surface. Since protein G has a specific interaction with the F_c portion of immunoglobulin G (IgG) [10], the paratope of IgG can face the opposite side of the protein G-immobilized solid support. The protein G-mediated antibody immobilization can lead to a highly efficient immunoreaction. The schematic of the antibody immobilization on the SPR surface by the SA technique is shown in Fig. 4.

The self-assembled monolayer of 11-mercaptoundecanoic acid (11-MUA) on the Au surface was fabricated by submerging the prepared Au substrate into a solution containing 11-MUA for at least 12 h. For chemical binding between the 11-MUA adsorbed on the Au substrate and the free amine from the protein G, the carboxyl group in 11-MUA was activated by submerging the Au substrate modified with 11-MUA into a solution of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC) for 2 h at room temperature. The self-assembled protein G layer was fabricated by the incubation of the activated Au substrate in a solution of protein G in phosphate buffer (PBS, pH 7.4) at room temperature for 2 h. To immobilize the antibody, the protein G layer formed by SA technique was immersed in a solution containing antibodies in a PBS buffer. After 4 h of incubation at 4°C, the surface was rinsed with a PBS buffer. In order to provide antigen access to the antibody binding site, separation of antibody molecules clustered around preferred points on the surface

or around other antibody molecules was achieved using Tween 20. The formation of protein G layer on the Au surface modified with 11-MUA and the binding of antibody and antigen in series were confirmed by SPR spectroscopy.

The effect of a detergent such as Tween 20 on the binding efficiency of antibody and antigen was investigated by SPR. The binding efficiency of antigen to the antibody immobilized on the Au surface was improved up to about 85% and 100% by using protein G and Tween 20, respectively. Consequently, an immunosensor based on SPR for the detection of *S. typhimurium* using protein G was developed with a detection range of 10^2–10^9 CFU/ml. The current fabrication technique of a SPR immunosensor for the detection of *S. typhimurium* could be applied to construct other immunosensors or protein chips.

Nanopattern Fabrication

Biomolecules immobilized on solid surfaces are useful in various areas of science and technology, including biosensors, biochips, chromatography, and diagnostic immunoassay. Biological units should be miniaturized for the integration and multiplication of these systems. The miniaturization offers several advantages, including cost lowering, simultaneous multicomponent detection, and the efficiency increase of biochemical reactions [36, 39, 44].

Owing to the advent of the post genome age, the importance of functional genomics has been increased. The basic goal of functional genomics is to understand how to fabricate functional proteins, cells, and organs. To get the information, the Southern blot method using gel electrophoresis separation was exquisite but needs a lot of time, and therefore, the development of new analysis tools is required. The DNA chip is a useful and versatile tool to get information for functional genomics. The basic principle of the DNA chip is as follows. A single-stranded DNA (ssDNA) probe can form a double-stranded and base-paired hybrid with ssDNA, if the probe sequence is the reverse complement of the target sequence. A DNA chip has arrays of reagent (oligonucleotide, cDNA) on the surface of a small plate of glass or other substrates [60]. The number of immobilized DNA is usually several hundreds to ten thousand. Florescence, which is produced by fluorescent-materials-tagged capture DNA, was observed by a florescence scanner to confirm the hybridization of target DNA and capture DNA. However, conventional DNA chips have severe problems in detection limit and analyzing to bind with target DNA. Nanotechnology has been applied to overcome these problems. A nanoscale array can fall in the limit of detection and decrease error-to-signal ratios. A label-free DNA chip using a nanowire or nanotube was developed and used for a direct real-time electrical detection of target DNA. The DNA chip consisting of multiple nanoelectrodes makes possible the multiple and extreme sensitivity detection of DNA.

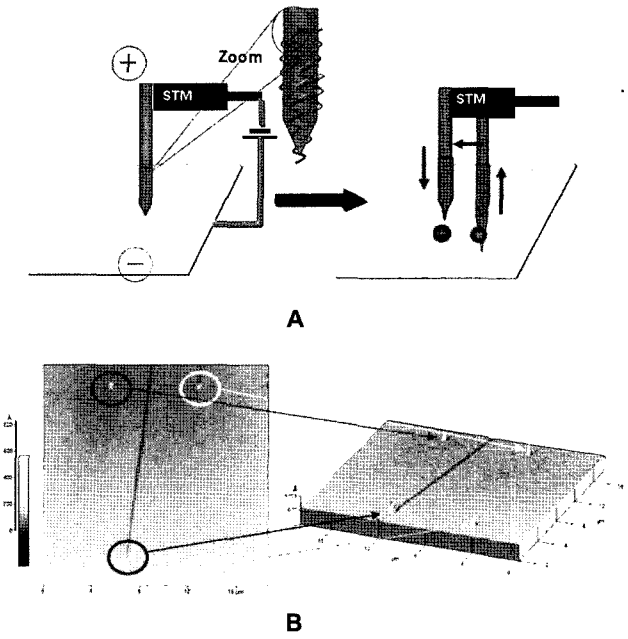

Fig. 5. Schematic procedure (**A**) of DNA nanoarray fabrication using STM and AFM images (**B**) of a 2×2 DNA array fabricated by STM.

In our recent research, the possibility of nano-DNA array was investigated based on nanopattern formation by STM (Fig. 5). Negative-charged DNA was picked up by using a positive-charged STM tip and then used to form DNA arrays. The average size of the immobilized DNA arrays is 400 nm. To amplify the response of the nano-DNA array, colloidal gold nanoparticles were used for the detection of the electrical signal.

The patterns of antibodies, which are important molecules for the diagnostic immunoassay, are essential for the miniaturized immunosensor system. Several patterning techniques such as photolithography, electrospray, ink-jet printing, and microcontact printing (μCP) have been used to fabricate the array of biomolecules [28]. Among the above mentioned techniques, the μCP technique is particularly attractive, because of its ability to deposit unlimited patterns and to permit the printing of multiple biomaterials in individual patterns [37]. Using the μCP technique, thiol groups or biomaterials are transferred from a stamp to a Au surface, and they are then attached to the substrate with SA adsorption. Several researchers studied the formation of antibody pattern on a solid surface, using μCP [54]. Based on these studies, the strategies for fabrication of antibody patterns can be categorized into two procedures. One procedure is the direct printing of antibody on a solid surface by using the poly(dimethylsiloxane) (PDMS) stamp. In this system, the reproducibility of the amount of adsorbed protein was poor, because proteins are physically adsorbed onto the Au surface. The other procedure is

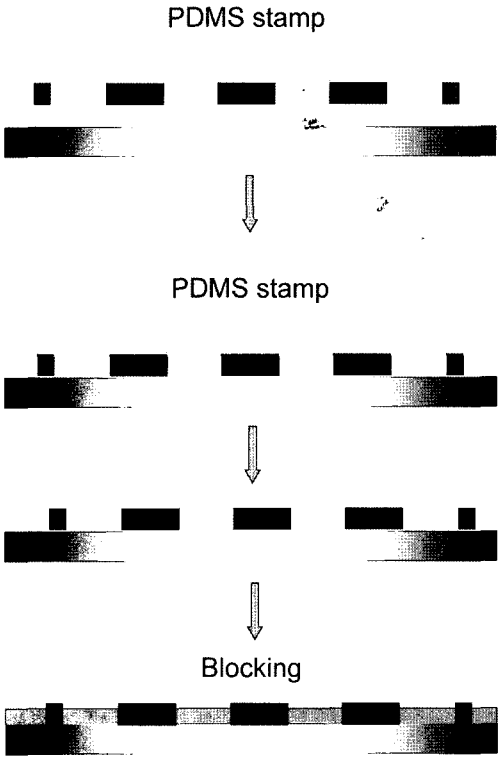

Fig. 6. Schematic procedure of microcontact printing method.

composed of pre-patterning of alkylthiolate on a Au surface and the protein binding on alkylthiolate pattern. In this procedure, the chemical immobilization of protein onto the alkylthiolate pre-patterning surface results in good repeatability.

Our research group recently reported making the antibody pattern for the immunosensor systems using μCP. In that study, a substrate, having the micropatterns of alkylthiolate on Au surface, was prepared by the μCP technique, and the antibody pattern on the template was fabricated. The schematic procedure of microcontact printing method is described in Fig. 6. The formation of antibody pattern on the substrate was performed by using the μCP technique, and the formation was confirmed by applying it to the antibody probe for detection of *Escherichia coli* O157:H7 [37].

Of many conventional patterning techniques, SPM-based lithography methods provide access to the smallest features (submicro-size array) [46]. Among the several SPM-based lithographies, dip-pen nanolithography (DPN) is considered as an attractive method for generating arrays with hundreds of features. Nanoscale biomolecular arrays can allow to do single-particle (protein, virus, and cell) study [47]. It is essential for single-particle study to nano-scale and directly deposit the soft matter, but most single-probe methods cannot fulfill these two requirements. However, DPN can be used to immobilize biomolecules such as proteins, DNA, and single virus on a substrate with high resolution [47]. Proteins have been deposited in nanoscale on gold and pretreated-glass substrates using this technique.

Microfluidic System

Microfluidic devices are defined as devices that control nanoliter amounts of fluids in microscale volume (1 nL= 100 μm×100 μm×100 μm). Such microfluidic devices like micromixers, micropumps, and microvalves, have currently been developed to realize nanotechnologies to commercial biodevices, for example, μ-TAS or nanoliter dosing systems [8]. The first commercialized microfluidic device by MEMS technology was inkjet print heads. This device can elute nanoliter-scale fluids though a micro nozzle by thermal expansion or piezoelectric force.

One of the most important issues to develop microfluidic devices is the selection of material, because surface effects become enlarged as the device is miniaturized. The materials for a microfluidic bio-device ought to consider by the following issues as well as process ability: 1) chemical stability or resistivity; 2) price, for disposable device to minimize contamination; 3) surface properties for biofouling; and 4) thermal stability for nucleic acid amplification such as PCR. Other properties, like optical transparency, can be preferred for testing modules. For example, for optical transducers, glass-utilizing devices are preferred over silicon devices owing to their optical properties. However, silicon still plays a leading role, not only as the electrical, but also as the mechanical material, as in atomic force microscope tips (AFM) because of well-established standard photolithography technologies including wet and dry etches (coupled plasma/reactive ion etcher like a Unaxis SLR 770 etcher, Fig. 7). The resulting features are used for MEMS and biological applications.

Various types of glass as well as silicon are used in microfluidic devices because they have several advantages such as electrical insulator, chemical stability, available micro machining process, transparency at certain

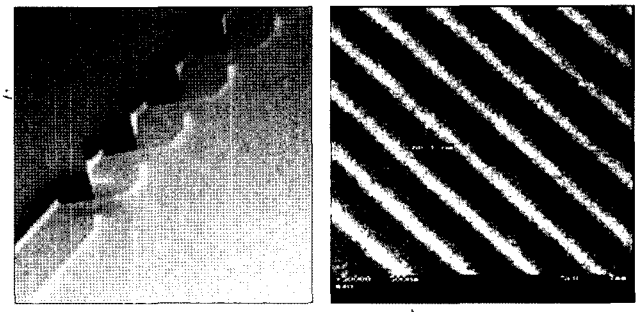

Fig. 7. SEM pictures of silicon structures fabricated by dry etcher: **A.** Fifty μm in height and 20 μm of narrow channel platform, **B.** Forty nm strips with 20 nm of depth.

wavelengths, and easiness of coating process with various chemicals [20]. A variety of different methods available to create channels in glass have been developed, since it is not possible to apply vertical etches to an amorphous material like glass [5, 19, 22, 29, 30, 48]. Photo-structurable glass composed of Li_2O-Al_2O_3-SiO_2 and doping agents (Ag, Ce, Sn, and Sb), developed by the Ilmenau Technical University [29], has been used to fabricate a capillary electrophoresis chip with modified photolithography technology [5]. The epoxy-based photo-resist SU-8, which has excellent sensitivity and high aspect ratios, has been utilized increasingly in microfluidic devices as an alternative to silicon [30, 48]. Good photoresistive properties of SU-8 gives rise to vertical sidewall profiles and hence good dimensional control over the entire structure height.

The elastomer polydimethylsiloxane (PDMS) has attracted attention as a material suitable for the easy and rapid fabrication of microfluidic devices [67] using soft-lithography. PDMS has a number of advantages: 1) features on the micrometer scale can be reproduced with high accuracy in PDMS by replica molding technique; 2) it is optically transparent down to 280 nm; 3) it cures at low temperatures; 4) it is not toxic; 5) it can seal reversibly to itself and a range of other materials by making molecular (Van der Waals) contact with the surface, or it can seal irreversibly after exposure to an air plasma by formation of covalent bonds; and 6) because it is an elastomer, it will conform to smooth, nonplanar surfaces, and it releases from delicate features of a mold without damaging them [20, 50].

The representative device in the microfluidic modules is the micromixer, which includes the mixing of several compounds such as buffer reagents, enzymes, and nucleic acid probes to create completely homogeneous solutions. The difficulty in mixing fluids on the microscale lies in the small size of the devices. Microfluidic devices that require a mixing operation have typically relied on diffusive mixing by bringing the fluid streams to be mixed together within a single channel. The small channel sizes and the lack of turbulence in microfluidic systems have thus led to the development and publication of several static and dynamic mixer designs, often operating under pressure-driven flow [6, 32, 63]. Miyake *et al.* [52] published a micromixer using a double-layer structure for mixing two liquids. Four-hundred nozzles were fabricated in the middle of a separating membrane, so one liquid could be injected into the second stationary liquid through these micronozzles. In a different mixing approach, the increase of lateral mass transport with very low lateral diffusion, and therefore several means of increasing the contact area between two liquids, has been investigated [42]. These mixers have multistage structures that can repeat the lamination/splitting process. Although the mixing capability of such a static mixer without external force to mix solutions may be affected by flow rates and the ratio of the flowing solutions, it is generally more robust and easier to implement than a dynamic mixer in which moving parts will have to be integrated [26, 68].

Using a simple analytical model, the flow in a "twisted pipe" has been studied [6]. The basic configuration consisted of a sequence of pipe bends, with successive bends oriented along different planes causing mixing, partly due to chaotic advection. The modeling showed very promising results and the design has been subsequently applied successfully to heat transfer enhancement on the microscale, by fabricating them in PDMS using micromolding and layered manufacturing techniques [1, 53].

In contrast to static mixers, the dynamic ones mimic their macro counterparts. Magnetic stirrers, for example, are the conventional dynamic mixer for achieving homogeneously mixing volumes on the order of liters. A tube vibrator mixer becomes the main tool for mixing volumes on the order of millimeters in the biological field [68].

A reliable active micromixer should be tolerant of gas bubbles, and the mixing effect should be adjustable by changing the level of an external input force [66]. Approaches using ultrasonic waves have increased recently [56, 68, 71]. Ultrasonic force by using lead-zirconate-titanate (PZT), a piezoelectric ceramics, can locally generate turbulence near the nozzles under certain conditions like high frequency operation [68]. However, ultrasonic waves generate substantial heat, which limits their application in bioanalytical systems in which a precise temperature control is required, such as with amplification and hybridization reactions of nucleic acid based biosensors.

A different active mixer was introduced by Tsai and Lin [63]. A microfluidic mixer with a gas bubble filter activated by a thermal bubble-actuated nozzle-diffuser micropump was successfully demonstrated. The oscillatory flow induced by the micropump generated a wavy interface between two solutions to increase the contact area of mixing fluids. The effect was demonstrated using a blue food dye and isopropyl alcohol. The alcohol was injected into the blue dye flow using a nozzle-driven thermal bubble pump. The motion generated by bubbles expanding and collapsing created the wavy interface between two liquids. Subsequently, the generated bubbles were removed by bubble filters consisting of narrow and wide channels, thus increasing the surface energy of the bubble when forced through a narrower channel.

In this article, we reviewed nanotechnologies in biodevices such as the nanoparticles for the detection of biomolecules, the immobilization of biomolecules at nanoscale, nanopatterning technologies, and the microfluidic system. Nanotechnology is revolutionizing the development of biodevices and it is increasingly being used to design novel biodevices with high performance. Unfortunately, little attention is being given to the study of the various nano effects that are actually their most attractive aspect.

New nanotechnologies need to be explored for use in biodevices. For example, nanotechnology-based biosensors should be integrated within tiny biochips with on-board electronics, sample handling, and analysis. This will greatly enhance functionality, by providing devices that are small, portable, easy to use, low in cost, disposable, and highly versatile diagnostic instruments.

Biodevices may grow rapidly in the 21st century. If a biodevice with high performance by nanotechnology could be developed, it can secure a monopolistic technological position in the worldwide market. Nanotechnology-integrated biodevices can contribute to stand the technologically advanced country through the creation of a high-value industry, which provides the synergy and motive for society.

Acknowledgments

This work was supported by the Core Environmental Technology Development Project for Next Generation funded by the Ministry of Environment of Korea and by the Korea Science and Engineering Foundation (KOSEF) through the Advanced Environment Monitoring Research Center at Gwangju Institute of Science and Technology, and by the Nano/Bio Science & Technology Program (M10536090001-05N3609-00110) of the Ministry of Science and Technology (MOST).

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