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Nanostructures in biosensor-a review

Se-Hyuk Yeom[1], Byoung-Ho Kang[1], Kyu-Jin Kim[1], Shin-Won Kang[1]

[1]School of Electrical Engineering and Computer Science, Kyungpook National University 1370 Sankyuk-dong, Bukgu, 702-701 Daegu, South Korea, 2School of Electronics Engineering, College of IT Engineering, Kyungpook National University 1370,Sankyuk-dong, Bukgu, 702-701 Daegu, South Korea

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1. ABSTRACT

In the 21st century, it is widely recognized that along with information technology (IT) and biotechnology (BT), nanotechnology (NT) will be a key field of science that will drive future developments. NT is expected to allow innovations in industrial fields such as electrical and electronics, biochemistry, environment, energy, as well as materials science by enabling the control and operation of materials at the atomic and molecular levels. In particular, the application of NT in the field of biochemistry is now enabling the realization of previously unachievable objectives.This review discusses the growth, synthesis, and biocompatible functionalization of each materials, with an emphasis on 1D nanomaterials such as CNTs, inorganic nanowires (made of Si, metals, etc.), and conducting polymer nanowires, along with 0D nanomaterials such as nanoparticles. This review also investigates the sensing principle and features of nanobiosensors made using the abovementioned materials and introduce various types of biosensors with nanostructure 0-D and 1-D. Finally, the review discusses future research objectives and research directions in the field of nanotechnology.

2. INTRODUCTION

In recent years, the provision of government funding in USA, Japan, and the EU has meant that considerable progress has been made in various aspects of the field of nanotechnology. In particular, industrial and academic scientists have focused their efforts on research and applications in the field of nanobiotechnology (Figure 1). Efforts in this field are geared toward developing new materials and devices through a detailed study of their operating properties at the atomic and molecular levels on the one hand, and studying human diseases and other biological processes and developing related products on the other hand. Because of the academic, commercial, and sociocultural importance of nanobiotechnology and the high expectations for revolutionary technological developments in the future, many countries worldwide are focusing their efforts on R&D in this field. It has now been roughly ten years since such efforts were undertaken. Therefore, although these are still the early stages, rapid developments have already been realized because of the positive support provided by various countries toward such research.

Table 1. Properties of SWNT and MWNT (4)

Properties	SWNT	MWNT	Comparison
Diameter (nm)	0.5~3.0	5~100	E-beam lithography; Line width: 50 nm
Tensile strength (GPa)	~100	<50	High strength alloy: 1~2
Young's modulus (TPa)	5.5	0.4~3.7	High strength alloy: 200 GPa
Density (g/cm^3)	1.33~1.40	1.40~1.60	Al: ~2.7
Resistivity (Ω·cm)	1×10^{-4}	$5.1 \sim 5.86 \times 10^{-6}$	Cu: 1.7×10^{-6}; in-plane graphite: 3.8×10^{-5}
Current density (A/cm^2)	~10^9	-	Cu: 10^6 A/cm^2
Field emission turn-on voltage (V/μm)	0.7~2	1~5	Mo tip: 50~100
Thermal conductivity (W/m·K)	Max. 6,000	Max. 3,000	Diamond: 3,300 W/m·K

Such technological developments have facilitated the development of nanostructures such as nanooptical fibers, nanoparticles, nanowires, and nanotubes, and researches on applying these to devices are proving quite successful because these devices can be used to manufacture high-speed, high-density, subminiature sensors, thus enabling the detailed analysis of very small quantities of specimens. The application of the abovementioned research to existing biotechnology suggests that, for example, it will be possible to develop chips such as DNA chips and protein chips that can be used for analytical purposes and for clarifying gene functions, which will help in clinical pathology and in developing new medicines. Biosensors improved using nanotechnology can detect materials at the molecular level using a high-speed and subminiature sensor for single-molecule detection (SMD) (1-3); such biosensors can prove to be beneficial for minimally invasive diagnosis, point of care, and early disease diagnosis. Such nanobiosensors can detect various types of biomolecules such as enzymes, antibodies, antigens, acceptors, and DNA. However, biosensors should also be capable of measuring slight changes at the molecular level from the bond between biomolecules and a specific molecule. This review examines nanomaterials in terms of their processing method and functionality and discusses their disadvantages relative to bulk materials, and it summarize how nanobiosensors can be applied to monitoring the metabolism and detecting cancer markers, and DNA. In addition, the review discusses possible future directions for nanobiosensors.

3. NANOSTRUCTURES AND NANOPARTICLES

3.1. Synthesis of carbon nanotubes (CNTs)

CNTs are one of the most interesting new materials that have been developed in the last 30 years. Their excellent properties have attracted considerable industrial as well as academic interest. A CNT is a tubular sheet of graphite that has a diameter of the order of nanometers. Carbon-based materials include diamond, graphite, and fullerenes. However, CNTs have a lower density and larger aspect ratio than all of these materials. CNTs also have a mechanical strength that is several tens of times stronger than that of high-strength alloys; electrical conductivity greater than that of copper; and thermal conductivity twice that of diamond; in addition, they have thermal stability at up to 750 °C in air. Because of these good features, the use of CNTs as a filling material is being actively studied in the field of nanocomposites. Currently, a polymer matrix is used in most CNT composites; however, many researchers are attempting the use of ceramic and metal matrixes as well. CNTs having various shapes can be formed using different synthesis methods and test conditions. Depending on the number of piles rolled using graphite sheets, CNTs are classified as single-walled (SW), double-walled (DW), and multi-walled carbon nanotubes (MWNTs). They are also classified as armchair, zigzag, and chiral depending on the rolling angle (Figure 2). CNTs having different structures exhibit different electric properties. With regard to conductivity, armchair nanotubes are metallic whereas zigzag nanotubes are semiconductors. An SWNT comprises a single rolled layer of graphite and has a diameter of 0.5~3 nm. A DWNT comprises two concentric rolled layers of graphite and has a diameter of 1.4~3 nm. An MWNT comprises 3~15 layers of graphite and has a diameter of 5~100 nm (4) (Table 1). The unique electric features of CNTs arise from the one-dimensional structure, the original electrical structure of graphite, and the extremely low electric impedance. The impedance of an SWNT is no more than 1/100 that of copper and its current-carrying capability is 1,000 times that of copper. With regard to mechanical properties, CNTs have very high hardness and strength because their structure comprises carbon–carbon sp2 bonds. Studies on the mechanical properties of CNTs have revealed that they have a Young's modulus of 5.5 TPa and tensile strength of 100 GPa (5–8). Relative to the respective values for high-strength alloys, 200 GPa and 1~2 GPa, CNTs have very good mechanical properties. The thermal conductivity of a CNT is twice that of diamond, the material known to have the highest thermal conductivity thus far. As mentioned above, CNT is ideal for application as a filling material in multi-functional composites because it has good electrical, mechanical, and thermal properties.

CNTs can be fabricated by various methods such as arc-discharge, laser vaporization, HiPCO (high-pressure carbon monoxide, chemical vapor deposition (CVD), and pyrolysis. Arc-discharge was initially used to fabricate CNTs. In this method, two carbon rods respectively serve as the negative and positive electrode. Carbon clusters separated by the collision of discharged electrons with the positive carbon electrode are condensed on the surface of the negative carbon electrode, following which they are cooled to a low temperature. A CNT is thus formed (9). Laser vaporization is a method proposed by Smalley *et al.* in 1995. In this method, graphite is vaporized using a laser and the vaporized carbon clusters are condensed and adhered to a Cu collector cooled to a low temperature. A CNT is thus formed. Relative to the arc-discharge method, this method has a higher yield and produces higher-quality CNTs (10). The HiPCO method was also proposed by Smalley *et al.* In this method, an SWNT is obtained by pyrolyzing a mixture of carbon monoxide and pentacarbonyl at high temperature

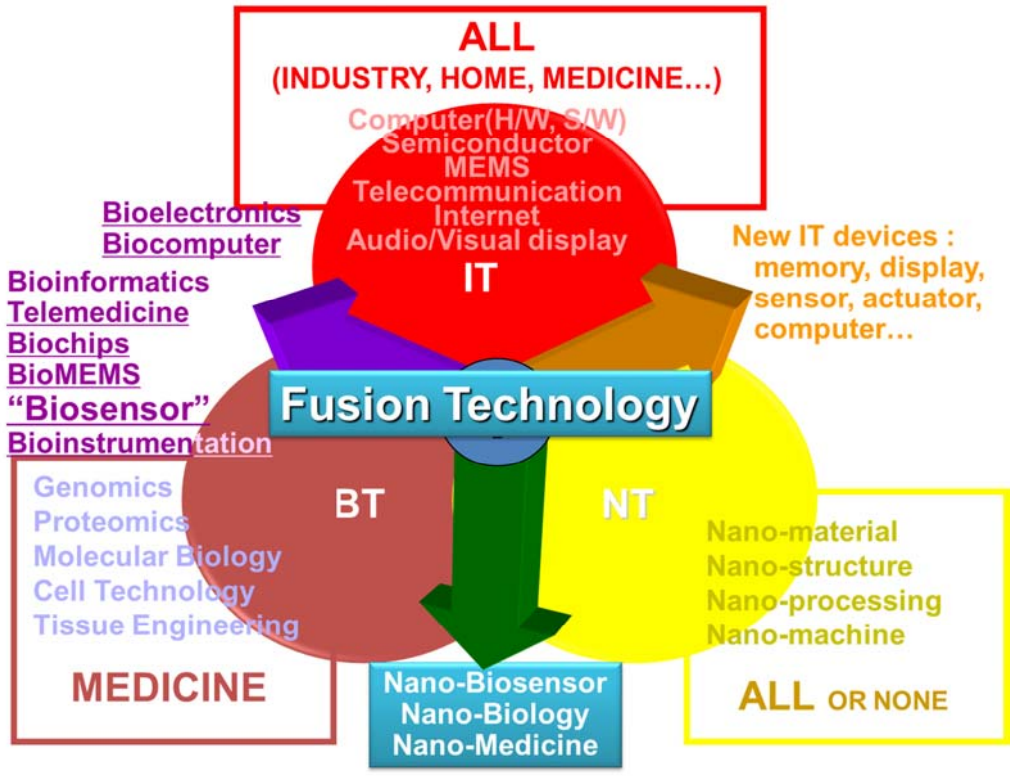

Figure 1. As a materials technology, nanotechnology has been considered as one method for enhancing traditional biosensor technology. Among NT, IT, and BT, the first has attracted most public attention from the viewpoint of the potential for future developments. For the development of high-sensitivity and multi-functional nanobiosensors, it is necessary to maximize the synergy between various technologies, i.e., Fusion technology, to realize improved device performance.

(800~1200 °C) and high pressure (5~10 mb) (11). An SWNT obtained by this method contains a smaller amount of amorphous carbon than that contained in a CNT synthesized by pyrolyzing a hydrocarbon in another manner. Two CVD methods can be used for fabricating CNTs: thermal CVD and catalytic CVD. The latter is advantageous in that it produces relatively larger amounts of high-purity MWNT with a fixed-bed reactor and a fluidized-bed reactor (12,13).

3.2. Synthesis of nanowire (NWs)

Nanowires are characterized by quantum confinement in the lateral direction. The characteristics of nanowires, such as large surface area, very high electronic density, high bond density of Van Hove singularities energy, high bond energy, radius-dependent band gap, high surface dispersion of electrons, and quantum effects, differ from those of a bulk material. An important characteristic of nanowires is that electron transfer is governed by one-dimensional (1D) quantum effect, unlike the 2D and 3D quantum effects that hold in bulk materials. Electron transfer in a low dimension is mainly classified into two types: ballistic and diffusive. Ballistic transfer occurs when an electron moves along a nanowire without any dispersion, whereas diffusive transfer depends on carrier dispersion within a nanowire by phonons (lattice vibration), boundary dispersion, structural defects that differs from the lattice, and impurity atoms.

Nanowires are typically synthesized by the vapor-liquid-solid (VLS) process. In this process, a catalytic liquid alloy phase is used to rapidly adsorb a vapor phase, following which crystal growth can occur to produce the solid component (14) (Figure 3). Processes such as laser ablation and chemical vapor deposition are often used for explaining synthesis technology in a special test and are used as a means to produce or transfer a vapor phase. A synthesis method with a template has recently attracted research interest. Template nanowire growth involves growing a nanowire within or on another nanosized structure. A vapor phase or liquid is solidified to the shape and size of the template through chemical reaction or cooling. The template is removed by etching, leaving behind only the nanowire. Electrochemical vaporization and melting permeation are generally used. The use of solution chemistry, lithography, and extrusion methods has also been reported. Nanowires can find increased applications if their sizes are enhanced and if they are synthesized using more convenient constituent materials. With regard to optical applications Bi nanowires are used for infrared absorption; ZnSe nanowires, for green light emission; and silver nanowires, for nanowire lasers that operate in the near-infrared region. Because of their good

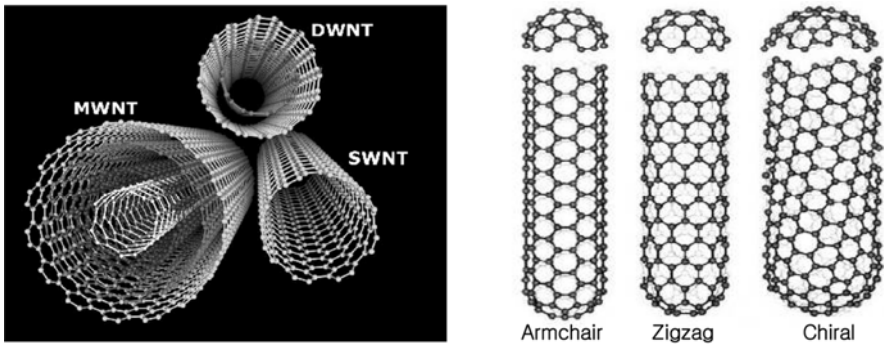

Figure 2. Types of carbon nanotubes.

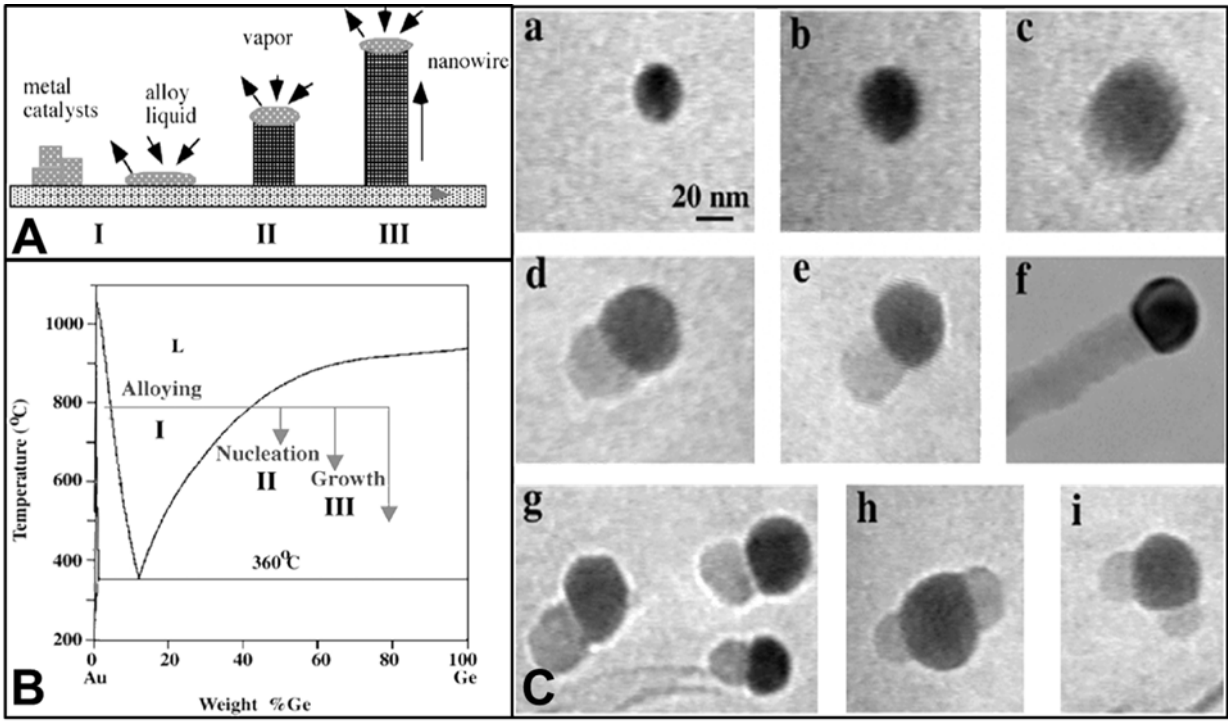

Figure 3. (A) Schematic illustration showing the growth of a nanowire via the vapor-liquid-solid mechanism. (B) Binary phase diagram between Au and Ge, where the compositional zones responsible for alloying, nucleation, and growth are indicated. (C) *In situ* TEM images recorded during the process of nanowire growth. (a) Au nanoclusters in solid state at 500 °C; (b) alloying initiates at 800 °C, at this stage Au exists in mostly solid state; (c) liquid Au/Ge alloy; (d) the nucleation of Ge nanocrystal on the alloy surface; (e) Ge nanocrystal elongates with further Ge condensation and eventually a wire forms (f). (g) Several other examples of Ge nanowire nucleation, (h,i) TEM images showing two nucleation events on single alloy droplet. Reproduced with permission from ref (14). Copyright©2001 American Chemical Society.

electrical properties, nanowire find numerous applications in nanoelectronics, thermoelectronics, and superconductors, and these properties are being further researched to realize newer applications. The electric properties of nanowires also make them ideal for applications in various types of sensors. In particular, their application in the field of bio- and life sciences has attracted considerable interest.

3.3. Synthesis of colloidal quantum dots (QDs)

Nanoparticles having sizes of the order of 10^{-9} m are larger than molecules or atoms but smaller than a bulk material. Nanoparticles having sizes controlled to approximately 1~20 nm have interesting features that differ from those of a bulk material. These features have been extensively researched in the last two years because they may lead to various novel applications. In particular, numerous researches have focused on semiconductor nanoparticles because the optical, electrical, and physical features of such materials change with the particle size. In a semiconductor nanoparticle, two main changes are observed with the particle size. First, if the size of nanoparticle decreases, the electronic energy structure of

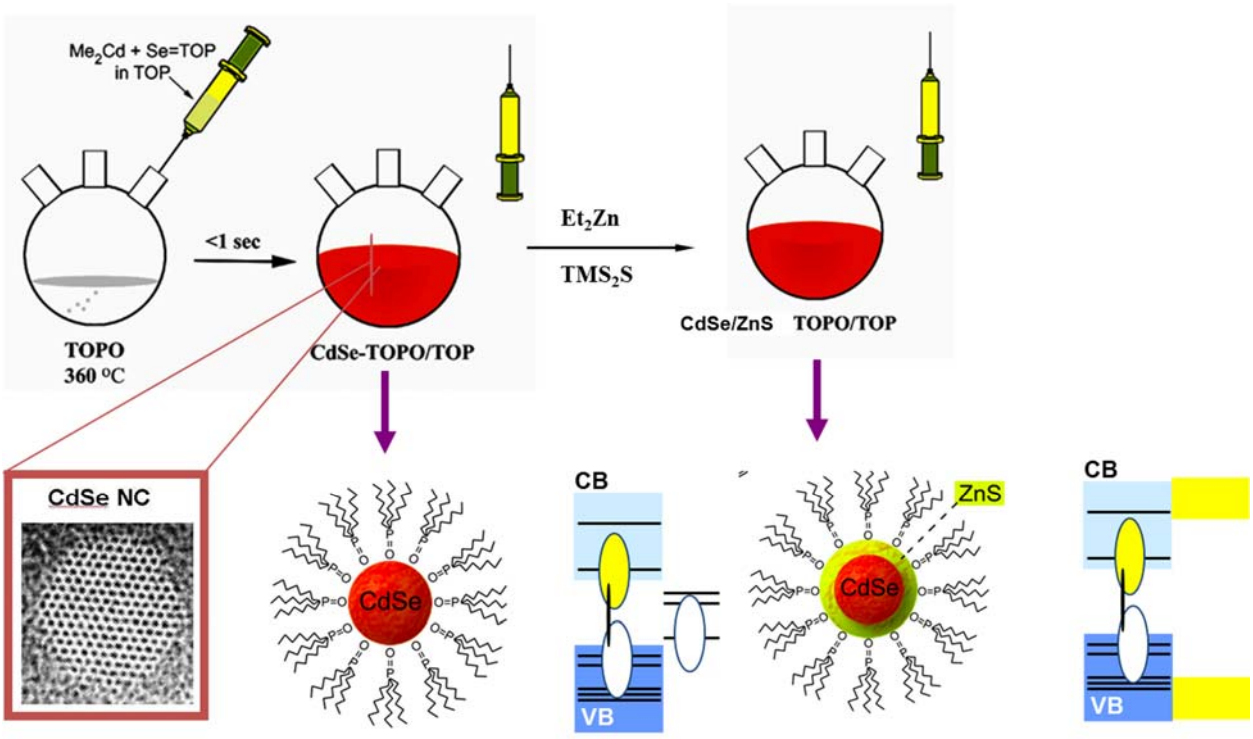

Figure 4. Synthesis of monodisperse CdE (E = S, Se, Te) nanocrystal semiconductor. Typical preparation of TOP/TOPO capped CdSe nanocrystal.

the nanoparticle changes. Also, the band gap (Eg) of the nanoparticle becomes large. Second, when the number of atoms on the surface is increased, the number increases to a greater extent as compared to the number of internal atoms and it largely depends on the surface features. These two differences strongly affect the optical features of nanoparticles.

Initially, numerous studies attempted the use of laser vaporization. When clusters having 3~50 atoms were obtained, a very distinct change was observed in the electronic structure. However, it was found to be difficult to carrying out a direct observation of the structural properties because it was impossible to mass manufacture a nanoparticle having a specific size. As a solution to this problem, scientists began studying 0-dimensional QDs, that is, a small nanocrystal in a liquid phase, unlike a large molecular cluster formed by a gas phase. Such researches resulted in the development of a method to cap ligands in order to prevent crumpling among crystals and to increase solubility. Among the various methods for synthesizing a representative nanoparticle, one is Bawendi's (1993) method of applying TOPO for capping a ligand. First, specimens such as Cd $(CH_3)_2$, Se powder, TOPO, trioctylphosphine (TOP), and Hexylphosphonicacid (HAP) were used for the above research. Although $Cd(CH_3)_2$ was previously used as a precursor to synthesize CdSe nanocrystals, it is difficult to handle because it is toxic and explosive, in addition to being expensive. Therefore, there was increasing demand for an eco-friendly and inexpensive precursor. Nowadays, $Cd(Ac)_2$ and CdO are commonly used for the abovementioned synthesis. TOPO, $[CH_3(CH_2)_7]_3PO$, is used as a metal extractor in other chemical engineering. This compound has three trigonalhydrocabon chains and exhibits local trigonal symmetry. It also exhibits a partial permanent dipole. This compound attains stability in a colloid by spatially limiting the crystal growth of a nanoparticle and by acting as a catalyst. Like HAP TOPO, this compound induces spatial limitation and its oxygen atom has a partial negative charge. Therefore, HPA is considered to be a stronger ligand than TOPO and is used along with TOPO. As a capping ligand that can be used with HPA, stearic acid can be considered. Fatty acids such as stearic acid can act as the catalyst required to cap the ligand reaction. To form CdSe, dissolve Se powder into trioctylphophine (TOP) to produce TOPSe. After preparing a stock solution, form a monomer by injecting it into the Cd stock solution and inducing crystal growth (Figure 4).

When $Cd(CH_3)_2$ exists in a TOPO solvent, a chemical change occurs in the pyrolysis, considering the fact that the given environment is very hot (300 °C). Namely, Cd metal exists as a Cd positive ion within the solution. Generally, when TOPO is used without a strong ligand such as HPA, Cd positive ions are reported to be precipitated into Cd metal. However, when HPA is used, Cd positive ions are reported to immediately change to Cd-HPA. The same applied for tetradecylphosphonic acid (TDPA). It has been reported that numerous tests use HPA and TDPA simultaneously. Such a reaction is like an M-Y reaction such that the ligand with the highest negative

partial charge within the solution may satisfy the coordination number of the metal positive ion after the M-X bond is changed to a positive M ion in the condition with sufficient heat energy. An investigation of the selection of the Cd precursor indicated that $Cd(CH_3)_2$ is not absolutely necessary. To prove the above, some groups tested various Cd precursors. As a result, they synthesized very good CdSe nanocrystals with varying degrees of success.

4. FUNCTIONALIZATION of NANOMATERIALS FOR BIOSENSORS

Functionalization is an important factor that defines the chemical properties and biocompatibility of 1D nanomaterials. The functionalization of 1D nanomaterials like biomolecule is gaining importance now that nanomaterials are being applied to biological applications. If the materials present at the molecular or nano levels have special physical properties, it becomes possible to miniaturize biological and electrical devices including probes and sensors when combined with good biological sensing ability. The contact scope between biological molecules and nanomaterials is very important in the above field of application. In this section, the review discusses the functionalization of CNTs, SiNWs, and metal nanowires.

4.1. CNTs and nanowires

The functionalization of 2D nanostructures is classified into two main types: covalent functionalization and non-covalent functionalization. Covalent functionalization is a chemical process in which a powerful bond is formed between 1D nanomaterials and a biological molecule or other links. For the active group to form a bond with the biomolecule, it is necessary to develop a process for the chemical treatment of the surface. The diimide-activated amidation reaction that is used to remove carboxylic acid is the most common method used to form a covalent bond on a 1D nanostructure. Another method is to functionalize a biomolecule with a 1D structure by covalently removing the amine. Unlike covalent functionalization, non-covalent functionalization does not destroy the geometric or electrical structure of molecules to bond them to a 1D nanostructure. A non-covalent interaction is an important factor in many biological systems, for example, a hydrogen bond between the 3rd complex structure and the complementary DNA helix structure of a protein. Hydrophilic and hydrophobic interactions are involved in the inactive absorption of surface proteins.

4.1.1. Carbon nanotubes

CNTs are generally functionalized by dispersing them in a liquid condition. The best method for preparing liquid CNT is the 1,3-dipolar cycloaddition of azomethine ylide. In this method, the original CNT floating matter included in dimethylformamide (DMF) is applied to N-substituted glycine and aldehyde. The bioactive peptide forms a covalent bond with SWNT through a stable bond formed by the partial condensation of the fragmented peptide. Azomethine ylides and SWNT created by such a chemical reaction are matched with the peptide (BM-COOH) by reacting with the N-terminal and O-(7-aza-N-hydroxybenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and diisopropylethylamine (DIEA) included in DMF. A peptide-induced CNT can be separated and its protective group can be continuously removed by bonding with TFA. To form a covalent bond of protein on CNT, the diimide-activated amidation reaction of CNT functionalized by carboxylic acid is generally used. It is also possible to connect CNT and DNA by removing the amine through carboxylic acid by the chemical action of diimide. Another method for removing the covalent bond between CNT and the amine is using the heterobifunctional cross-linker succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC). In the above process, to form carboxylic acid at the end part and the boundary part, the refined SWNT is oxidized. To remove the amine, the CNT is reacted with thionyl cloride and ethylenediamine. Then, only the surface is left with a maleimide group by applying the amine to the SMCC. Finally, a DNA-removing thiol is used to obtain a DNA-treated SWNT by reacting with the above group.

A CNT can realize covalent functionalization by the reaction of the oxidized carboxyl group with DNA-removing bovine serum albumin (BSA) protein and amine through the diimide-activated amidation reaction reported by Sun *et al.* (15,16).

On the other hand, Matsui *et al.* developed a method to functionalize CNT and avidin only at the end of a nanotube with a Au nanocrystal as a protective mask at the side of the nanotube (17). Nanotube masking with a Au nanocrystal absorbs avidin on the surface. On the other hand, the chemical etching of a Au nanocrystal mask can only be carried out at the end of the nanotube by removing the acidin molecule in the side wall. The process of chemical etching does not degenerate avidin and the end of the nanotube is fixed to the SAM layer of a complementary biotin.

To prevent the formation of a protein bond, Dai *et al.* reported the functionalization of detergent and SWNT with the absorption of poly(ethylene glycol). This method was found to effectively resist the unspecific absorption of streptavidin (18). The streptavidin structure forms a specific bond with SWNT, and this could be realized by functionalizing biotin and a protein-resistant polymer with CNTs. Polyethylene oxide (PEO) links have been used to supplement a specific bond of a nanotube (19). For example, a specific bond of protein on a nanotube can be overcome by fixing a PEO link. Another non-covalent protein fixing technology was also announced by Dai *et al.* In this method, a protein is irreversibly reacted by absorbing 1-pyrenebutanoic acid succinimidyl ester, a molecule with two functions, with the SWNT (20).

4.1.2. Si/Metal nanowires

Silanization is widely used for SiNW surface deformation. Before surface deformation, the SiNW surface is subjected to vapor plasma treatment. The plasma cleans the nanowire surface and creates a hydrophilic surface by forming a hydroxyl-terminating silicon oxide surface. The hydrated layer is activated using organosilane, a reactive

group. The target biomaterial is covalently bonded using one among various different methods. First, aldehydes are removed from the SiNW by reacting with 3-(trimethoxysilyl) propyl aldehyde. Next, the deformed nanowire completes a covalent bond between the biomaterial and SiNW by reacting with the biomaterial in the presence of sodium cyanoborane (21–23). In another method, the SiNW fixes the biomaterial deformed by acrylic phosphoramide after reacting with 3-mercaptopropyltrimethoxysilane in Ar atmosphere. This technology was used for the functionalization of DNA probe deformed with acrylic phosporamide at SiNW and 5N-end (24).

Recently, photochemical hydrosilation has been used such that DNA and SiNW exist freely and in a functionalized state without disturbing the oxide (25). In this process, SiNW-removing hydrogen forms a covalent bond with 10-NBoc-amino-dec-1-ene through UV catalyst reaction (26). The removal of the t-BOC protection group leaves a major amine that forms a covalent bond on the SiNW surface. The DNA-removing thiol forms a covalent bond with the amine in the presence of SMCC, a heterobifunctional linker.

Martin *et al.* reported another functionalization of silica nanotubes with two types of silane molecules on the internal/external surface by deforming the internal surface of the nanotube with the first silane within the pore of the template sensing film (27). The external surface contacts the inner wall of nanotube because it contacts and masks the pore wall. The template is dissolved to separate it from the unmasked external nanotube surface and a nanotube is exposed to attach the second silane on the surface of the external nanotube. It is possible to attach antibodies or other biomaterials on the silane surface. The covalent deformation of the nanostructure has a disadvantage in that it degrades the physical properties despite the existence of a very strong bond. Many covalent functionalization processes involve multiple stages and high-concentration acids and powerful oxidizers are often used for surface treatment.

Mallouk *et al.* reported a usable DNA functionalized nanowire to make a block for surface assembly (28). Single-strand DNA (ss-DNA) is coated by reacting with gold nanowire to form a heterogeneous structure material. Using a microscope, it can be confirmed that the bond to the gold nanowire was four times stronger than that with an ssDNA functionalized surface.

Biological functionalization can also be applied to nanostructures. Metal parts can be used for optional spatial functionalization depending on the length of the nanowire because they have different surface features (29). The optional functionalization of Au/Pt/Au nanowire with Pt and Au is reactive with thiol and isocyanide. It substitutes 2-mercaptoethylamine (MEA) on Au, but not on Pt, to form a butaneisonitrile monolayer on the Au/Pt/Au wire surface. The gold part supported by MEA in a nanowire is marked by a fluorescent display molecule to obtain a SAM image indicating spatial localization according to the length of the nanowire.

As another example, Ni-Au nanowire is discriminatively functionalized by thiol, a long-link-removing palmitic acid, and hexa(ethylene glycol) (30). Ni surface is functionalized to palmitic acid. On the other hand, Au surface is functionalized to alkanethiols and terminal hexa(ethylene glycol). When exposed to a fluorescent display protein, hydrophilic Ni wire emits light, but a Au-wire removing EG-6 doe not. This implies that a protein is not attached to the EG-6 nanowire. Ni-Au nanowire with alkyl and EG-6 surfaces is exposed to fluorescent protein. The fluorescence image indicates that only Ni is observed in the wire and the protein is optionally absorbed in only a part of the multi-component nanowire.

4.1.3. Conducting polymer nanowire

A conducting polymer nanowire is a new material used in ID chemical sensing and biosensing. The advantage of a CP nanowire is that an unrefined reactant can be manufactured easily through well-known chemical or electrochemical processes. Their conductivity can be increased by an order of 15 by changing the ratio of the dopant or the monomer/dopant. A CP nanowire can be functionalized before/after synthesis using methods that differ from those used for Si or metal nanowires. The main advantage is that SiNW and CNT devices requiring functionalization and arrangement after synthesis bond with functional biomolecules within the CP nanowire at once and the synthesis progresses with internal electrical contact.

Most researches on the functionalization of a conducting polymer are based on thin films. However, such researches can also be applied to conducting polymer nanowires. Various functional groups can be immobilized by a CP parent. Such a process may enable the development of a material that induces a combination of features because of the CP and its functional group. As mentioned above, CP functionalization can be performed at three stages: before polymerization, during polymerization, and after polymerization.

The functionalization of a CP nanowire before polymerization initially involves the covalent bond of a specific group of a monomer. Then, the preparation of the functionalized polymer progresses. For example, it is possible to replace the process of attaching hydrogen to nitrogen in pyrrole with a specific group. It is possible to apply such a method to cases in which a specific group has a stable feature during polymerization.

Among various processes for polymerizing CP nanowires, functionalization is one in which specific anions are bonded by static electricity during electric polymerization. Such a method can realize functionalization because anions doped into the polymer parent are irreversibly caught. Thus, the bonding of the complex negative ion ligand with the CP progresses. For example, Wang *et al.* studied the bonding of CNT with polypyrrole through direct electrochemical synthesis with a template (31). PPy becomes shorter and acts as an anti-ion with a charge by being electrically vaporized into the pore of a major sensing film with carboxylated CNT dopant. The flow of electrons within the synthesized nanowire is

accelerated by the CNT. In this review, a test was carried out to produce an amperometric enzyme electrode based on the bond of a CNT dopant with glucose oxidase (GOx) in one stage within an electric-polymerized PPy thin film with a group and process similar to that mentioned above (32). The CNT dopant continues to act as an electric catalyst to provide high sensitivity by being restrained within the PPy network. Therefore, the bond of CNT and GOx forms at once and affords biocatalytic and electric catalytic features to the amperometric transducer. Thus, this provides a simple and effective method for forming an enzyme electrode.

Functionalization after the polymerization of a CP nanowire is a process in which a proper function group within a polymer makes a covalent stable bond with other function groups of specific molecules. Such an approach requires CP electric synthesis with a reactive entity used as a support to apply a functional group. A good example of the same is the post-polymerization functionalization of poly (N-substituted pyrrole) thin film (33).

Additionally, there exists a method to confine a goal molecule within CP to fix a target material during the process of electrochemical polymerization. In this method, a working electrode is dipped in a solution containing the target molecule, monomer, and dopant, and a suitable voltage is then applied. However, the catalysis and adaptability of a fixed biomaterial such as an enzyme observed in a polymer thin film are often reduced quickly because of physical restrictions and steric inhibition (34,35). On the other hand, this method has an advantage in that the restriction of molecules occurs without any chemical reaction. For example, it was recently reported that biomolecule were restricted within a CP nanowire by a quick and convenient method (36). In this process, avidin was restricted during the process of electrochemical polymerization within the PPy. It was allowed to progress only at a certain stage within a channel of 100 nm connecting two electrodes. As a result, avidin functional CPNW controlling dimension was obtained, and it had a high aspect ratio. Similarly, Mallouk *et al.* manufactured a gold-capped and protein-deformed PPy nanowire with a porous Au oxide template (37).

4.2. Colloidal quantum dots

To apply colloidal QDs to biological applications, it is necessary to disperse them into water through the chemical substitution of the surface, and not an organic solvent. This is realized by replacing TOPO with a ligand that can easily disperse, such as mercaptoacetic acid, mercaptopropionic acid alc dihydrolipoic acid (DHLA), DL-cysteine, as well as thiolated acid.

4.2.1. Fluorescent Analysis of QDs

Traditionally, QD has been widely used as a bioindicator with antibodies. It has low SNR for fluorescent dye and sensitivity to photobleaching. Therefore, an analytical system combining QDs with various other cell components and a toxin was developed. In such systems, an antibody is attached to the surface of a deformed polyacrylamide (AMP) coating QD through a functional link such as sulfo-SMCC (38). In another method, an antibody is attached to an adaptor protein fused on the QD surface.

Such a fusion process has been used for the detection of staphylococcal enterotoxin B(SEB) on a plate based on an assay, and for an immune measurement system to detect 2,4,6-trinitrotoluene (TNT) in a solution specimen (39). QD with a narrow fluorescent emitting spectrum has been extensively researched, and various toxin assays using an antibody combined with QD have been developed (40). In another antibody fusion method, a biotinylated antibody attached to QD is used through interactions with acidin or streptavidin. QD fused with avidin has been used as an assay to fuse with biotinylated antibody to detect SEB and chlorella toxin (41). Pegilated streptavidin fusion has been used as an immune sensor for the development of a cell microassay, detection of malignant cell protein (42,43), detection of sulfamethazine surviving in chicken muscle cell (44), and detection of prostate-specific antigen (45). An antibody fused with QD has been applied to detect respiratory cell fusion virus (46). In this test, protein (G) attached with virus fusion (F) to a cell sensing film is used as an antigen marker of RSV infection. Because of the improved sensitivity and SNR afforded by the QD probe, the test results can be obtained within 1 h after infection and the infection can therefore be detected in the early stage. A special protein detection test or PCR that are currently used for clinical tests require four days to detect an infection; however, anti-viral treatment is effective only in the early stages of infection. Consequently, QD can be applied to rapidly test for RSV and various other infections in the field of clinical diagnosis.

QD combined with antibody can be applied to complex protein detection tests that require extremely sensitive and quantitative detection (47,48). Although a fluorescent QD with a controllable size was restricted by QDs that produced different colors with different analysis materials, an antibody fused with a single-color QD enables the realization of various assays. Therefore, an antigen/antibody immune complex has two different colors. For example, BSA and BSA antibody (lgG) were fused with QD (49). A fluorescent immune assay was developed to detect human estrogen receptor-β (ER-β) with Forster resonance energy transfer (FRET). In this assay, a QD with a 565-nm fluorescence was used as a FRET donor, and multi-cloned anti-ER-β was used as an acceptor by being marked with Alexa Fluor® 568 or Alexa Fluor® 633 dye (50). A method was developed to detect Listeria monocytogene, an important food-borne virus, with Internalin A (In1A) and Internalin B (In1B) facilitating cell infection. A fixed cell specimen was observed through a fluorescent microscope with major anti-ln1A and detected biotinylated secondary antibody and streptavidin QD (51). FFPE lymphatic grand cell and tonsil organization could be observed by fusing QD fused with streptavidin with a suitable antibody and various biotinylated secondary antibodies (52). Finally, Purkinje cell fixed to formalin within gliadin was used as a marked in a cerebellum cell with a specific antibody for glial fibrillaray acidic protein (GFAP) (53).

4.2.2. Functionalized QDs with peptide

A peptide can potentially act as a target ligand in the field of biological applications because it is much smaller than an antibody. This size difference enables a peptide to attach from at least ten to hundreds of units on one QD surface. Consequently, QD fused with peptide has a stronger combined affinity and produces the same effect as mixing various germs by providing better sensitivity to the target. It is possible to fuse various peptides with QD, and these peptides can be used to observe a live cell image. Peptide-based QD may pave the way for applications such as material-restricting angiotensin II with angiotensin I receptor (54), biotinylated epidermal growth factor (EGF) detecting erbB/HER acceptor. and QD fusing nervous growth element with TrKA acceptor within PC12 cell.

Cai *et al.* reported that fusing a pegilated cadmium telluride QD with argininеglycine-aspartic acid (RGD) peptide could be applied to imaging integrin αvβ3-benign tumor vasculature within a living body (55). Integrin αvβ3 plays an important role in the angiogenesis and transfer of a tumor and is considerably up-regulated by penetrating a cell in a specific cancer form (most tumor vasculatures such as glioblastoma, melanoma, breast cancer, ovarian cancer, and prostate cancer), but not in endothelial cell or the general organization. Integrin in an endothelial cell controls cell transfer in vasculogenesis and the control of integrin αvβ3 causes tumor regression by controlling tumor growth. Various methods are being developed to control integrin αvβ3 and the ability to image such acceptors within a living body can potentiality be very useful for cancer imaging and surgery. Near-infrared QD can be functionalized by attaching thiolated derivatives of peptide RGD on CdTe pegilated QD surface with an SMCC link. Thiolated derivatives of RGD can be synthesized by applying lysine ε-amino residues to S-acetylthioglycolic acid N-hydroxysuccinimide ester (SATA), and thiol protection can be removed from a neutral condition with hydroxylamine. By injecting the fusions into a mouse with U87MG tumor, it was observed that fusions could increase tumor cells more quickly than background fluorescence. It was observed that QD was accumulated in the liver, spleen, bone marrow, and lymph nodes.

Recently, in the field of cancer therapy, peptide fusion QD with specific heat shock protein as a target have been used to potentially replace cancer call imaging. Heat shock proteins are a group of protective proteins that are involved in processes within cells and outside cells, including protein synthesis, folding, microcystic exchange, and appearance and progress of antigen. Proteins that control glucose belong to such a group and are usually located in the cytoplasm reticulum. However, in a tonic condition exposed to heat, the manifestation of such protein is increased and it has a structure like a surface sensing film in the restricted form of a glucose-controlling protein. In addition, the extra manifestation of such protein is considered to be an attractive target for delivering alternative materials in chemotherapy for cancer therapy. It is known that various other cycling peptides are restricted to such proteins and are absorbed by cancer cells. One such peptide, Pep42, is covalently attached on a QD surface coating deformed by amphiphillic polyacrylamide (AMP) with EDC coupling. The restriction and absorption of such fusion within semi-stable human melanoma Me6652/4 or Me6652/56 cells has been investigated by FACS analysis (56).

Phage-display peptide related data were obtained to classify the continuous reaction of peptide with high affinity for a cell target. For example, as one such application, various cells restricting tetrameric peptide TP H1299.2 were reported and used for fusing with streptavidin QD to enable the imaging of live H1299 cell (57). Features with high affinity and specific targets for α4β1 integrin acceptor were reported with phage-display peptide data. The endogenous ligand of α4β1 integrin acceptor is QIDS and the motive of ILDV of fibronectin and vascular cell adhesion molecule-1 (VCAM-1). Such acceptors in endothelial cells increased in vasculogenesis during tumor development, and these are a good target for imaging in cancer therapy. When one synthesis is used in one bead combination chemistry, diverse peptide mimetics with high affinity are observed; two such syntheses include LLPIA and LLP2. The restraint affinity of LLP2A and LLP2B for α4β1 integrin acceptor can be measured using an adhesive assay controlling α4β1, jurkat cell, and fixated CS-1 peptide (25-amino acid linear peptide of fibronectin reacting to α4β1 integrin acceptor). It was found that IC50 of LLP2A and LLPIA was 2 ± 1.4 pM and 22 ± 18 pM, respectively. Next, a biotinylated version of LLP2A was used for imaging jurkat cells manifesting α4β1 integrin acceptor that were cultured within a cell in which biotinylated LLP2A and QD 605 fusion exist. LLP2A biotin was also used for imaging within a living body and it showed the strong coherence of Molt-4 cell manifesting α4β1 integrin acceptor when fused with streptavidin-QD (58). Zhou *et al.* developed a peptide-marking QD for the imaging of G protein coupled with acceptor in a live cell. In this system, they jointed a peptide with carboxylic acid on a QD surface by using EDC coupling and an SMCC cross link. The QDs are coated with low-weight molecules (~1200 Da) such as a diblock polymer surrounding acylic acid as a hydrophilic material and an amino-octyl forming side-chain with a hydrophobic component. Two other types of peptides were used to introduce distinct characteristics. NDP peptide is an α-MSH analog with high affinity for human melanocortin acceptor. Deltrophin-II analog is a specific material for δ-opioid acceptor. After fusion is completed, QD is used to mark live HEK cell manifesting NDP acceptor or CHO cell manifesting δ-opioid acceptor (59).

4.2.3. Functionalized QDs with small molecules

Rosenthal *et al.* reported for the first time that small-molecule fusion QD could be applied to the biological imaging field (60). They used a QD to image serotonin transmission (SERT) followed by surface deformation of pegilated serotonin ligand (61). Direct attachment on a QD surface is carried out through the end of a thiol. Such fusion neutralizes IC50 of 115 μM and SERT protein and simplifies the fluorescent imaging of SERT manifestation in HEK-293 cell infection. On the basis of their success with such serotonin ligand fusion, Tomlinson *et al.*

synthesized various ligands for dopamine transmission (DAT) and 5HT2A with SERT as a target. These were fused with QD by using various methods such as biotin-streptavidin interaction, EDC coupling on AMP dot surface, and thio exchange reaction of QD fused with mercaptoacetic surface. They expressed the contents of the selections of such syntheses. They continued to test biological targets with such ligands and revealed that they were biologically active (62–66). In addition, they found pegilated muscimol derivatives reacting specially to GABAC acceptor as a target. Gussin *et al.* studied AMP QD fusion and reported that pegilated muscimol derivatives could be used for imaging the manifestation of GABAC from Xenopus Laevis oocyte. It was reported that QD fusion specifically marked GABAC manifested from oocyte and AMP QD almost never had an effect on the unspecific marking of cell infection and B-cell infection oocyte (67). With their research in the scope of small-molecule fusion, Clarke *et al.* reported a method to fuse dopamine derivates with a QD surface through acid-based fusion chemistry and that small-molecule fusion was used for the fusion of a target cell in D2 acceptor (68). Such fusion is easily absorbed by D2 manifesting HEK293 and 3T3 cell, which is more than 10 times the numerical value of free dopamine. The result of the study includes contents related to the formation of dopamine quinine complex and observatory results related to cell toxins. Dopamine experiences optical insensitive oxidation to form quinine. This synthesis is toxic and damages more than 90% of the cell. However, when mercaptoethanol is added, the general cell survival ability and marking ability can be increased by reducing the component to control quinone formation. In addition, Clarke *et al.* reported that energy transfer processes occurred because molecules close to the QD surface induced the creation of free radical like 102 by acting as sensitive systems. Consequently, the oxidation damage of such dopamine fusion on cell systems can ultimately be applied to QD photodynamic therapy (69).

4.2.4. Labeling biomolecules

Antigen, antibody, and biomarking molecules as DNA with nanoparticles play increasingly important roles in developing high-sensitivity electrochemical biosensors. The measurement of fragment ions with fragments of nanoparticles as marking materials—most metallic or semiconductor nanoparticles—and stripping voltammetry represents general procedures of electric analysis technology, and stripping voltammetry is very strong electrochemical analysis technology for measuring metals (70).

Metal nanoparticle marking systems can be used as immune sensors and DNA sensors, with gold nanoparticle being used most frequently for this purpose. For example, Limoges *et al.* reported an electrochemical immune sensor with gold nanoparticles to measure immunoglobulin G (lgG) of a goat (71). Preferentially, they fixated anti-goat lgG of a donkey on a microwell surface and reacted it with goat lgG. They then added anti-goat lgG of a donkey marked with gold nanoparticles. They obtained oxidative fragments of the gold nanoparticle solution by treating the complex with acidic bromine-bromide. Gold ion with high solubility is reduced electrochemically and is detected by anodic stripping voltammetry with a carbon-based screen-printing electrode accumulated from the electrode. The detection of gold ion with high sensitivity using anodic stripping voltammetry and a combination of separating many particles by fragmenting gold nanoparticles through only one process helps in detecting goat lgG with 3 pM concentration. Applying an electrochemical method similar to the above, Limoges *et al.* developed a high-sensitivity DNA sensor with 20-nm gold nanoparticles and oligonucleotides as a marker to detect 406-based human cytomegalovirus DNA order in 5 pM concentration (72).

Silver nanoparticles and specific core-shell metal nanoparticles are being used as biomarking molecules for electrical analysis. It was reported that oligonucleotide could be detected at low concentrations of 0.5 pM using electrochemical DNA biosensor based on silver nanoparticles as a marking material (73). Fang *et al.* developed an electrochemical DNA sensor to detect high-solubility Cu2þ through anodic stripping voltammetry using nanoparticles with a gold shell at the oligonucleotide and a copper core by using 5'-alkanethiol as a marker (74). Similarly, Wang *et al.* reported a process for monitoring DNA crossbreeding on the basis of electrochemical stripping detection with ion tracking function (75). They separated nanoparticles including iron after DNA crossbreeding with core-shell nanoparticles of an iron core structure coating with gold as a DNA marker, and measured ions through cathodic voltammetry with catalysts of 1-nitroso-2-naphthol ligand and bromate.

Semiconductor nanoparticles have been widely used as markers in the field of electrochemical biosensors. In particular, they have been applied to DNA sensors (76). For example, thiolated oligonucleotide with CdS semiconductor nanoparticle as its marker was used for detecting DNA crossbreeding results (77). In this review, 1 M of CdS nanoparticle was separated and its result acts as an electrical signal to analyze DNA. On the basis of a similar principle, Wang *et al.* developed a method to analyze other DNA target materials at once (78). Three other types of nucleic acids were crossed with other DNA target materials by fixing to other magnetic particles. DNA probes were crossed with complementary DNA materials after being respectively marked with ZnS, CdS, and PbS nanoparticles. The stripping voltammetry of each separated semiconductor nanoparticle metal ion produced good results (Zn: -1.12 V, Cd: -0.68 V, and Pb: -0.53 V). Therefore, it is possible to carry out a simultaneous and high-sensitivity electrochemical analysis using these DNA materials.

In specific situations, oxidative nanoparticles can also be used as biomarkers. Fang *et al.* reported that they used SiO_2 nanoparticle doped tris(2,2'-bipyridyl)cobalt(III) [Co(bpy)3þ3] as a marker for oligonucleotide and applied it to the electrochemical detection of DNA crossbreeding (79). Co(bpy)3þ3 doped nanoparticle forms a double-standard DNA with the probe by a complementary DNA feature when the target DNA is fixed to a glassy carbon electrode by being used as a marker for the DNA probe.

After removing the uncrossed DNA, Co(bpy)3þ3 can be detected in SiO_2 nanoparticles by performing differential pulse voltammetry. At this stage, SiO_2 nanoparticles exhibit a distinct electrochemical response and can be detected at low concentrations (0.2 nM) of the target oligonucleotide.

An electrochemical biosensor using a nanoparticle marker is generally based on the final detection of the nanoparticle itself. Therefore, it is important to prepare for and apply specific nanoparticle markers. For example, when using specific synthesis with a core including specific material for use as shell as a specific marker or one that is easy to detect by an electrochemical method, it is important to develop high-sensitivity DNA sensors and immune sensors.

4.2.5. Live cell assay based on QD and antibody

In a sandwich assay, an antibody fused with QD has been used as a marker for live and fixed cells. A specific marker for live cells with QD and biotinylated antibody fused with avidin has been reported for the detection of infecting HeLa cell to express the extracellular course of P-glycoprotein(pgp), a multidrug transporter (80). In the test, Dahan found that the glycine acceptor of a live cell could be marked with a major antibody (mAb2b), biotinylated anti-mouse Fab specimen, and streptavidin fusion QD (81). In live Her2 cell, it can be used as a cancer marker (82). In PC12 cell, it can be marked as a TrkA acceptor (83). Single bacteria pathogens such as E. coli DH5α (84) can be marked with antibody and streptavidin fusion QD. In addition, SiHa cell can be marked with QD fusing anti-EGFR with streptavidin. Such fusion can be used for the early diagnosis of cervical cancer (85). The narrow fluorescent emitting spectrum of QD can be used for flow cytometry. Recently, Chattopadhyay *et al.* reported that they could simultaneously detect 17 other types of fluorescent emissions corresponding to specific antigens in T-cells with QD fluorescence (86). QD fusing streptavidin and QD coating amphiphillic polymer have been used for marking biotinylated antiCD33 antibody and detecting bone marrow, umbilical cord blood, and leukemia with flow cytometry (87). In addition, fluorescent assay with biotinylated antibody and streptavidin fusion QD have been developed. These have been used for detecting Escherichia coli 0157:H7 and Salmonella Typhimurium (88). Antibodies as well as such cell-based assay have been used for imaging tumors within the living body by being fused with QD (89).

5. APPLICATIONS OF NANOMATERIALS IN BIOSENSING

5.1. Nanostructures for biosensors

It is very important to understand life sciences and to develop devices that can be applied to detecting low-concentration biomolecules. In addition to providing biological information, biosensors can be used to diagnose and predict diseases and help in the development of preventive medicines. System biology requires the comparison of double analysis materials of biosamples with high-efficiency test equipment. Therefore, recent advancements in minimized biotesting systems are useful from the viewpoint of genetics, protein genetic information, and pharmaceutical technology. These developments could reduce the cost of diagnosis, detection, and medicines and lead to effective treatment with high-efficiency detection. The miniaturization of detection tools for complex detections must be pursued with the introduction of new technology. The development of strong, sensitive, and high-efficiency biosensors is an important issue in the field of nanobiotechnology (90–93). Thus far, for partial biological detection, immune-assay-based vaporation (94) and protein-test-based nanoparticles (95) have been used.

Nanostructured materials have been used for the detection of various protein molecules. One such example is cancer marker protein detection. Cancer marker proteins are molecules in blood or the organization that are related to cancer. It is useful to detect and measure such molecules to support patient diagnosis and clinical care. Recent researches have revealed that nanostructured materials are sensitive to such markers and are useful for real-time detection. For example, Lieber *et al.* reported very sensitive and complicated detection of cancer marker proteins with SiNWs (22). The modification of the cancer marker antibody array is less than 50–100 fg/mL. It is possible to realize real-time multi-detection of free protein specific antigen (f-PSA), PSA-a-antichymotrypsin (PSA-ACT) complex, carcinoembryonic antigen (CEA) and mucin-1. In undiluted serum samples, it is possible to measure targeted cancer markers with a concentration of less than 0.9 pg /mL optionally and sensitively. PSA antibody bond make p- and n- type nanowires functional in a single sensor for the differentiation of electrical cross-talk and false-positive signals, making it possible to detect PSA by proving the correlations of results from two types of devices. Real optional binding events provide a complementary result in p- and n- type devices. The variation of electrical conductivity in the two devices is similar and agrees with concentration-dependent conductance measurements. Recently, a complementary result to p- and n- type devices was presented by Zhou (96). In_2O_3 NW and SWNT mat surface made a PSA antibody functional. Continuous electronic detection of PSA increased the conductivity of the In_2O_3 nanowire and reduced the conductivity of the SWNT under exposure to PSA, with sensitivity of less than 5 ng /mL. (97)

An SiNW FET device is being used for the detection of small-sized molecules. For example, the detection of inhibitors, a small-sized molecule of ATP combined with Abelson protein (Abl), was attributed to the covalent bond of SiNWs (98). The constitutive activity of Abl, a tyrosine-protein kinase, is involved with chronic myelogenous leukemia. Gruner *et al.* used carbon nanotubes and no-scale field-effect transistors to detect Biotin-streptavidin binding (99). A polymer coating layer was adopted to avoid general binding with the attachment of vitamin B complex to a layer for specific molecule cognition. Streptavidin binding and vitamin B complex were detected electrically from the change in the FET device features. Chen *et al.* detected human self-antigen UIA less than InM with mAbs functionalized SWNTs (100) (Figure 5). UIA is a sample of a self-immune reaction of patients with systemic lupus

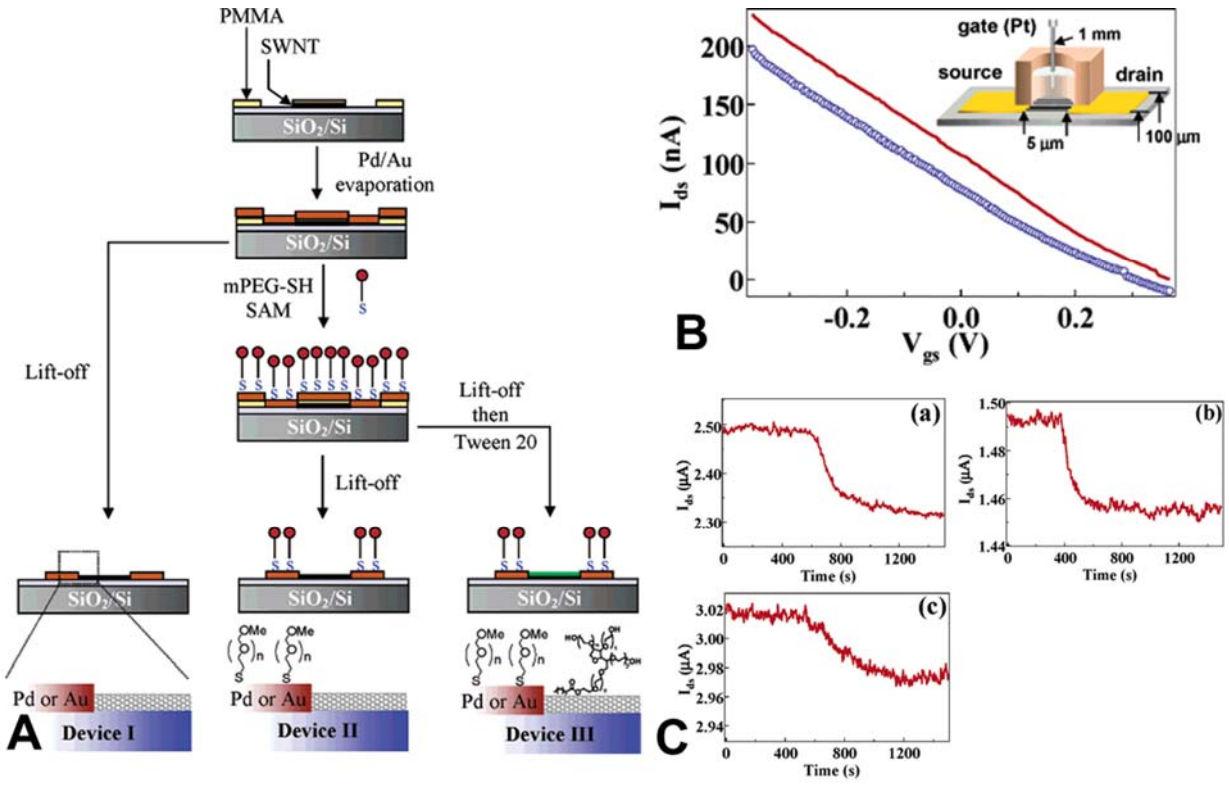

Figure 5. (A) Schematic flowchart of microfabrication processes for preparation of devices. (B) The semiconducting nature of micromat nanotube devices can be probed with current (I_{ds}) *vs. gate voltage* (V_{gs}) *measurements (bias = 10* mV) via a platinum wire top gate electrode inserted into the solution (inset). The main panel shows I_{ds} *vs.* V_{gs} *before (solid line) and after hCG desorption* (circle) on a type I device. A downward shift in the overall conductance is seen after protein adsorption. It should be noted that a device with an I–V_{gs} curve exhibiting near-depletion (zero SD conductance at +350 mV *Vgs) was* specifically chosen for this particular measurement. This near-depletion arises from a larger-than-usual ratio of semiconducting to metallic nanotubes bridging the electrodes, also resulting in a lower conductance overall. Typical devices generally used for other measurements exhibit higher conductance because of a relatively higher proportion of metallic nanotubes. (C) Electrical conductance change in type I devices upon nonspecific binding (NSB) of 100 nM (a) hCG, (b) hIgG, and (c) BSA in aqueous solution. Upon rinsing (data not shown), the conductance does not recover to initial values, indicating that protein adsorbs irreversibly on the devices. Reproduced with permission from, ref (100). Copyright©2003 the National Academy of Sciences USA.

erythematosus and mixed connective tissue disease. The electrical effects in the metal-nanotube contact revealed that protein absorption contributed more significantly to the electrical biosensing signal than absorption (101).

SiNWs have also been used for the direct detection of DNA. First, the surface of an SiNW device was changed to a PNA acceptor and perfect complementary verification of discordant DNA was carried out at least 10 times in at femtomolar concentrations (102). Second, Si nanowires were fixed in a covalent bond to detect single stranded (ss) probe DNA not labeled in a sample solution having a concentration of 25 pM (103).

Viruses are one of the main causes of human disease, and therefore, people have a higher interest in them because they can be used to carry out germ warfare and biological attacks. Lieber *et al.* used SiNWs for real-time electrical detection of single virus particles with high selectivity (104). Measurement with SiNWs made as a specific antibody against Influenza A virus detected the influenza A virus, and not paramyxovirus or adenovirus. In addition, SiNWs made as a specific antibody against these viruses could be similarly used to detect many other viruses.

Direct real-time detection of glucose was realized by SWNT glucose oxidase (GOx) changed from an FET device by monitoring the change in conductive power binding the glucose enzyme (105). On the other hand, Tao *et al.* used conductivity polymer nanojunction sensors to detect glucose (106). GOx was induced to polyaniline by electrochemical polymerization and it was used to catalyze glucose oxidation on being exposed to glucose. The reduced form of GOx recycled through re-oxidation by O_2 to create glucose. H_2O_2 can be used to oxidize polyaniline and increase polyaniline conductivity. Because of the small size of the nanojunction sensor, GOx is naturally recycled without requiring an oxidation reduction intermediary. Therefore, it provides a very quick result (<200 ms) and consumes some oxygen.

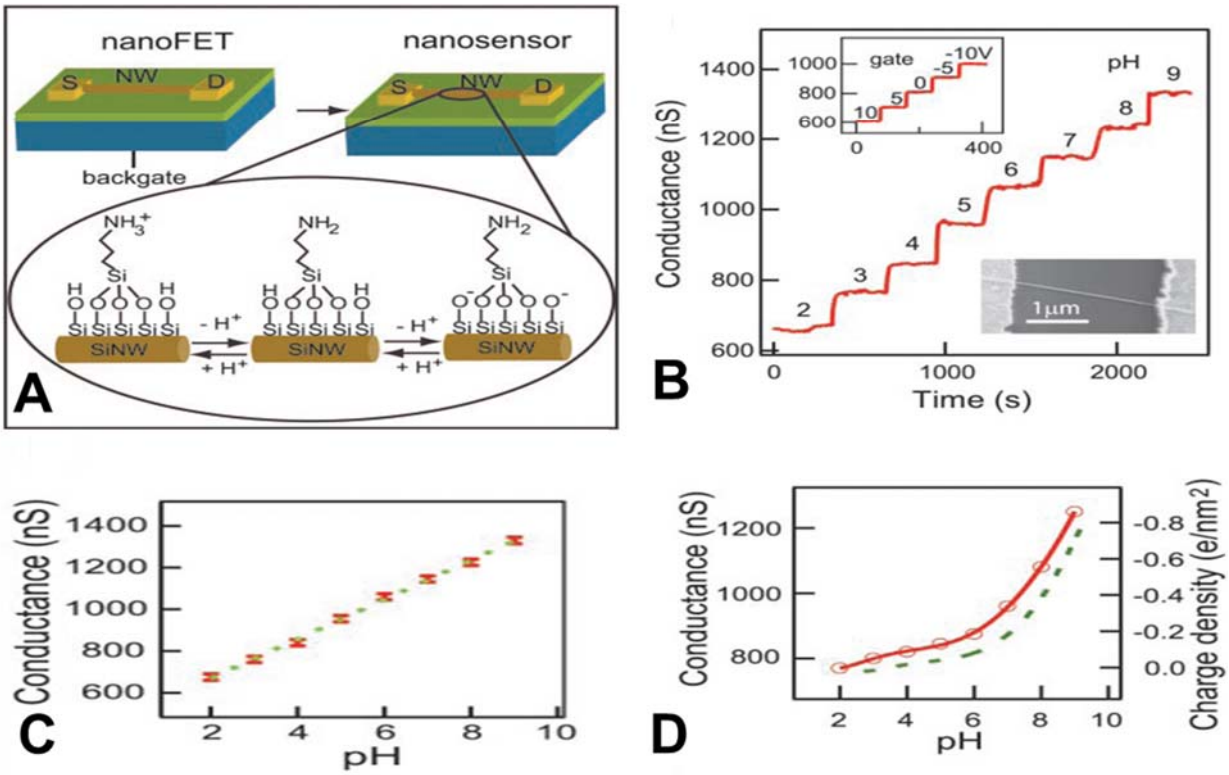

Figure 6. NW nanosensor for pH detection. (A) Schematic illustrating the conversion of a NWFET into NW nanosensors for pH sensing. The NW is contacted with two electrodes, a source (S) and a drain (D), for measuring the conductance. Magnified view of the APTES modified SiNW surface illustrating changes in the surface charge state with pH. (B) Real-time detection of the conductance for an APTES-modified SiNW for pHs ranging from 2 to 9; the pH values are indicated on the conductance plot. (inset, top) Plot of the time-dependent conductance of an SiNW FET as a function of the back-gate voltage. (inset, bottom) Field-emission scanning electron microscopy image of a typical SiNW device. (C) Plot of the conductance versus pH; the red points (error bars equal 6 1 SD) indicate experimental data, and the dashed green line indicates the linear FET data. (D) The conductance of unmodified SiNW (red) versus pH. The dashed green curve is a plot of the surface charge density for silica as a function of pH. Reproduced with permission from ref (107). Copyright©2003American Ass-ociation for the Advancement of Science.

Lieber *et al.* developed a nanobiosensor with nanowires for the first time; theirs is the most advanced technology in this field thus far. They developed a sensor that carries out measurements at the nanometer scale using Si nanowires. Their sensor has very good selectivity and can realize very-high-sensitivity protein detection because it has a large volume and surface area (107) (Figure 6). In addition, Dekker *et al.* developed a method for producing an FET-structure with carbon nanotubes that is similar to that used for producing Si nanowire biosensors (108).

5.2. Nanoparticles for biosensors

Mirkin *et al.* reported a new method for applying nanoparticles to biosensors, unlike existing fluorescent or electrochemical methods, for detecting DNA and proteins. The developed technology introduced gold nanoparticles on an electrode and induced the flow of electric current by reintroducing silver particles. Then, the target oligonucleotide was separated and detected from the difference of one base by measuring the change in the resistance value of both electrodes according to the hybrid version (109). The group also developed an innovative DNA sequence detection technology to detect four mutants at once, beyond the current technological limitation of detecting only one mutant, by developing gold nanoparticles (30 nm) with DNA barcodes. This technology is highly important next-generation technology that will be applied to multiplexed systems in the future. Using this method, DNA and proteins can be detected at respective concentrations of hundreds of zetomoles (zM, 10^{-21}) and attomoles (aM, 10^{-18}) (110).

As a study on developing optical sensors with single nanoparticles, Duyne *et al.* developed a single-particle-based localized surface plasmon resonance (LSPR) to detect hexadecanthiol particles with zM sensitivity (111). As another study on developing sensors with single nanoparticles, Raschke *et al.* developed a single nanoparticle optical sensor to detect 50 streptavidins with 40-nm gold nanoparticles reformed by biotin. It is expected that this sensor will be applied to the detection of virus, bacteria, and other microorganisms in water in the future

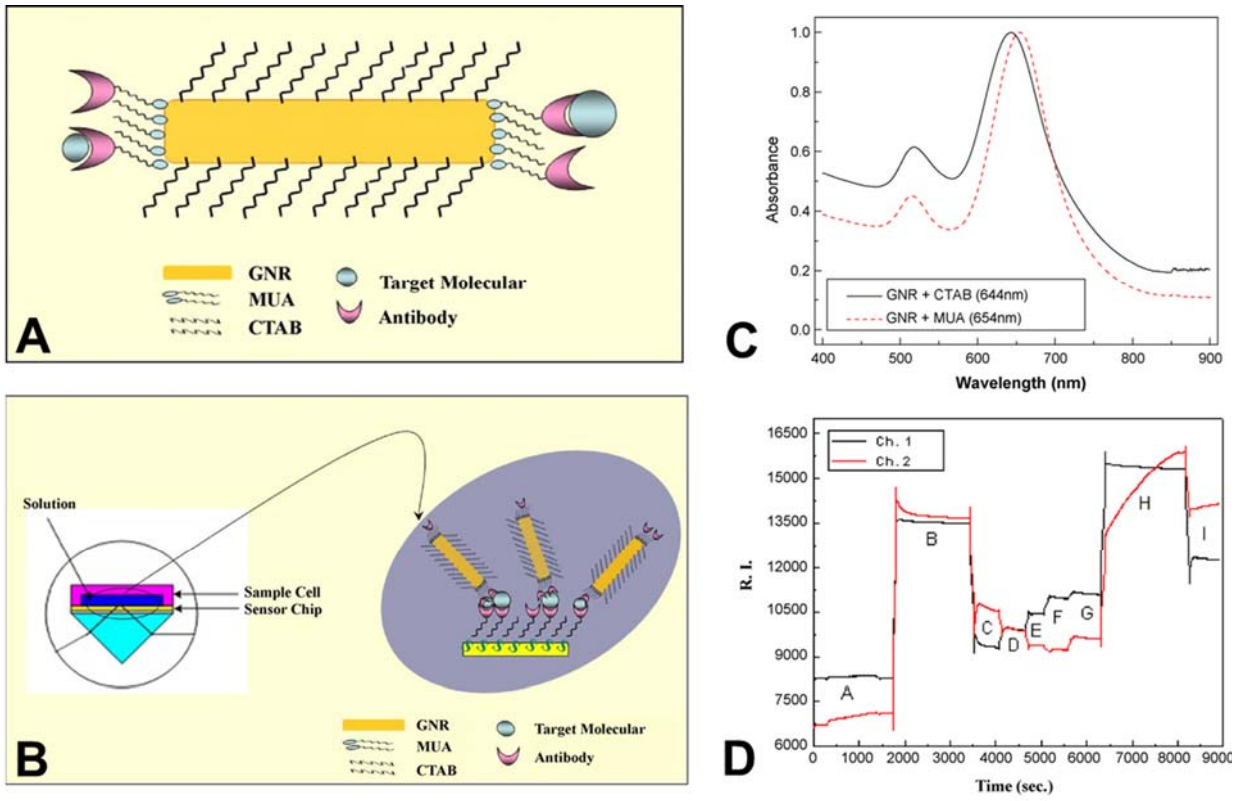

Figure 7. (A) Schematic diagram of gold nanorod molecular probe. (B) Schematic diagram of combined target molecule and antibody with GNR in SPR sensor. (C) Absorption spectrum of GNRs with CTAB and MUA induced by longitudinal plasmons. (D) Sensogram of refractive index changes during sensing surface absorbance. (A) PBS, (B) primary antibody, (C) PBS, (D) BSA, (E) PBS, (F) E. coli, (G) PBS, (H) GNR unlabeled antibody in channel 1 and GNR labeled antibody in channel 2, and (I) PBS. Reproduced with permission from ref (113). Copyright©2010 Elsevier.

(112). Our group developed a biomaterial measurement system using Au nanorods. This system measured E. coli O157:H7 on the basis of the principle that the variation in the dielectric constants was higher than that in the conventional method (only antibody) when the Au nanorod conjugated antibody was bonded on the sensing membrane. This system exhibited a sensitivity that was 3.8 times greater than that of the conventional measurement method. This method realizes improved sensitivity relative to other biosensor systems and related applications such as photothermal therapy (113) (Figure 7). Liu *et al.* manufactured a colorimetric nanosensor by reforming a gold nanoparticle surface with Pb ions; this affected the nanoparticle binding and the color of the nanoparticles changed to green from red when they formed a cluster by drawing near each other (114,115).

Cao *et al.* detected DNA and RNA by using surface enhancement Raman scattering (SERS) nanobiosensors with gold nanoparticles (116). The sensor could detect at concentrations of even 20 fM (1 femtomole = 1×10^{-15}) using a gold nanoparticle probe labeled by Raman active dye and oligonucleotide. From the viewpoint of environmental applications, such a biosensor will be quite useful because it could be used to detect pathogens in water. Kopelman *et al.* developed the PEBBLEs (Probe Encapsulated by Biologically Localized Embedding) nanobiosensor that includes a dye that makes the fluorescence disappear by the detection of a nanosized old element (117).

Halas *et al.* announced the development of a nanobiosensor to obtain specific chemical information for the first time. The developed sensor used the optical features of a metal nanoshell having a diameter of the order of tens of nanometers as a form of a nanoparticle. This technology can precisely control the electric and optical features of the nanoshell, and it can be widely applied in the field of biosensors in the future. In addition, it is expected that it will be applied to cancer detection (118).

A research team at Massachusetts Hospital, USA, developed a sensor based on magnetic iron oxide nanoparticles that produces a signal when cell extinction progresses with cancer therapy (119). On the other hand, a research team at the molecule imaging research center of Harvard University announced that they successfully detected viruses in the human organization using a nanoparticle sensor (120).

Su *et al.* developed a high-sensitivity sensor that effectively increases the mass and size of a molecule with

immunogold silver staining (IGSS) using gold nanoparticles for catalysis to reduce silver ions to metallic silver (121). Ishihara *et al.* developed a nanoparticle sensor for simultaneous diagnosis and therapy by fixing antibodies and enzymes on a surface-reformed nanoparticle surface after concentrating a polar group of phosphatide on the nanoparticle surface.

The mechanical research institute of Hitachi, Ltd. Japan, developed a small-sized device to analyze the interaction among biomolecules using a nanoparticle-based biosensor. This device can measure protein binding by injecting at most four nanoparticles into a disposable sensor cell and can monitor the interaction of the dissociation in real-time. This device can measure surface plasmons using nanoparticles having a diameter of 100 nm with a gold thin film on the surface as a biosensor. The particles exhibit unique colors depending on the resonance field (localized surface plasmons) at the nano level and they are discolored when a micro material (e.g., protein) is absorbed on the surface. They measured the color change in the reflected light by combining the protein on the surface of the sensor and measuring the binding amount. This device can measure the bonding of biomolecule in real-time because it does not require marking and does not require a prism, unlike the requirements of conventional surface plasmon resonance. We can analyze the interaction by measuring the color change in the nanoparticle using the device. Therefore, it is expected that this device will largely contribute to the R&D of proteomes because it is simple, small, and cheap.

The use of nanoparticles in biological detection improves the signal sensitivity of sensors because various electronic and optical features are controlled by the diameter and size of the nanoparticle (122). The partial chemical features of nanoparticles differ from the chemical features of bulk materials, and generally, nanoparticles are more chemically active than the corresponding bulk material because of their high surface energy. For example, MnO_2 nanoparticles directly react with H_2O_2. On the other hand, bulk MnO_2 catalyzes H_2O_2 decomposition (123). A remarkable electrochemical analysis system can be constructed by using the active features of nanoparticles and applying the nanoparticles to a special reactant. On the basis of the special reactivity of MnO_2 nanoparticles, Chen *et al.* developed some electroanalytical systems (124–127). A glucose biosensor manufactured by coimmobilizing glucose oxide enzyme and MnO_2 nanoparticles in the gate of an ion-sensitive field-effect transistor (ISFET) produced a high pH increase followed by an increase in the glucose concentration; this was essentially different from the pH change of conventional ISFET-based glucose biosensors (124). The pH change in the ISFET-based glucose biosensor is attributed to the formation of gluconic acid in biomembranes. On the other hand, that in the proposed biosensor is attributed to the special reaction of MnO_2 nanoparticles with H_2O_2.

Additionally, a semiconductor QD such as CdSe is used for bio-indication as a detection specimen in microscope observations, DNA chips, calculation of blood corpuscles, and immunity measurement (128). Such nanocrystals have good ability to exhibit simple excitations, making it possible to simultaneously measure multicolor and multielement. Therefore, QD-based bead based technology enables multiplex measurement. This is very useful for proteomics, genotyping, and gene expression studies. The floating arrangement with nanocrystals is a very good example of high-efficiency detection applications of the bead-based approach (129). Furthermore, microbead-based measurement have some advantages such as non-washing process of even the microarrangement, multi-measurement with protected microbeads, signal amplification because of the large surface-to-volume ratio, and short measuring time because of the free movement of microbeads within the medium (130,131). Another application field of QDs is molecular imaging. The technology can be applied to the imaging of living cells and imaging within the body (132).

Bawendi *et al.* reported a method for analyzing the organization and organs within a living body using InAs (ZnA) QDs. This method checks the organization and organs by sensing elements within various living cells after coating QDs with PEG chains having various lengths (133) (Figure 8). It is possible to carry out high-resolution observations of diverse organizations and organs (e.g., liver, kidney, pancreas, lymph, etc.) depending on the length of the PEG chain (2~22 units). They also inspected vasculature tumors using core-shell InAs (ZnCdS) QDs. The emitting wave of the manufactured QDs is 700–900 nm and the group diagnosed vasculature tumors using a near-infrared detector after the QDs combined with the vasculature tumors.

5.3. Various nanodevices for biosensors

Many researchers have studied signals followed by an electronic charge by cell combination to imitate the human nose or tongue since Persaud and Dodd first reported an electronic nose in chemical sensor and pattern cognitive form in 1982.

Morgan, Roach, *et al.* developed a device that was more than 1000 times as sensitive as the existing electronic nose. The developed device can detect hormones, diagnose diseases, and even detect bombs (Science Daily). Dai *et al.* developed a detector made using an SWNT to detect low concentrations of gases. This device was polymer coated with microspot technology to improve the detecting function. Through this process, the detector sensitivity to a specific gas was improved considerably; the device could detect nitrogen dioxide at a concentration of 10~50 ppm in a gas mixture.

Dai *et al.* predicted that the developed technology would play a large role in the development of next-generation very-high-sensitivity optional nanodetectors that could monitor housing or industrial environments and be applied in the fields of chemistry, medical science, and even for military purposes (134). Stetter *et al.* developed a portable device to detect, classify, and monitor poisonous gases in concentrations of the order of ppm (135). This prototype device used four current monitoring sensors

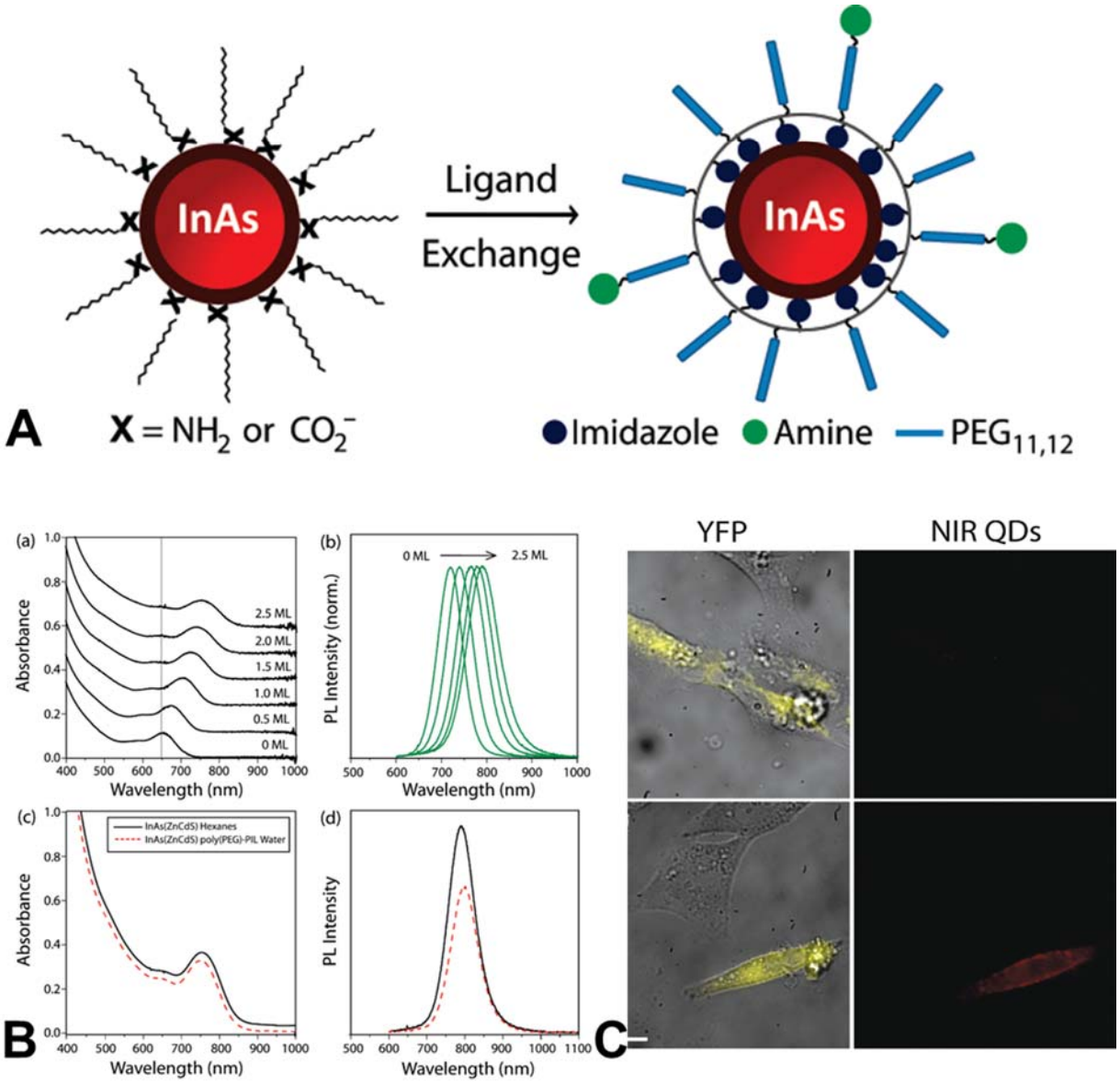

Figure 8. (A) Ligand exchange of organic soluble QDs with poly(amino-PEG11)25%-PIL to enable water solubilization. (B) (a-b) absorbance and PL of InAs(Zn0.7Cd0.3S) during shell growth from 0–2.5 monolayers (MLs). (c-d) Absorbance and PL (λmax, 795 nm; fwhm, 82 nm) of InAs(Zn0.7Cd0.3S) in hexanes (black) and after ligand exchange with poly(PEG12)-PIL (red) in PBS at pH 7.4. (C) HeLa cells expressing yellow fluorescent protein (YFP) fused to a biotinylated peptide presented on the extracellular membrane. (a) Streptavidin-QDs preblocked with biotin did not bind to the cell surface, whereas (b) nonblocked streptavidin-QDs are bound to the surface of YFP expressing cells (scale bar, 10 μm). Reproduced with permission from ref (133). Copyright©2010 American Chemical Society.

operated by four other modes. The developed sensor can practically detect 22 harmful gases using 16 sensors. This system can be applied to the quality classification of grain in the future (135–136).

Knake, Hauser, *et al.* manufactured a portable gas array by connecting a current sensor and a voltage sensor in series or in parallel to measure SO_2 and NO (137). Zhou *et al.* developed a solid electrolyte microcurrent sensor having an electrode diameter of 30 μm to detect CO_2 gas, and used a thin-film gas sensor with a solid electrolyte as a potential measurement sensor. If the sensor developed by this technology can be miniaturized in the future, it can be applied to an electronic nose system (138) (Figure 9).

Arntz *et al.* and a research team at the IBM Zurich Research Institute studied biomolecule compositions or roles and developed a biosensor by making a cantilever array having a size less than a millimeter that was coated

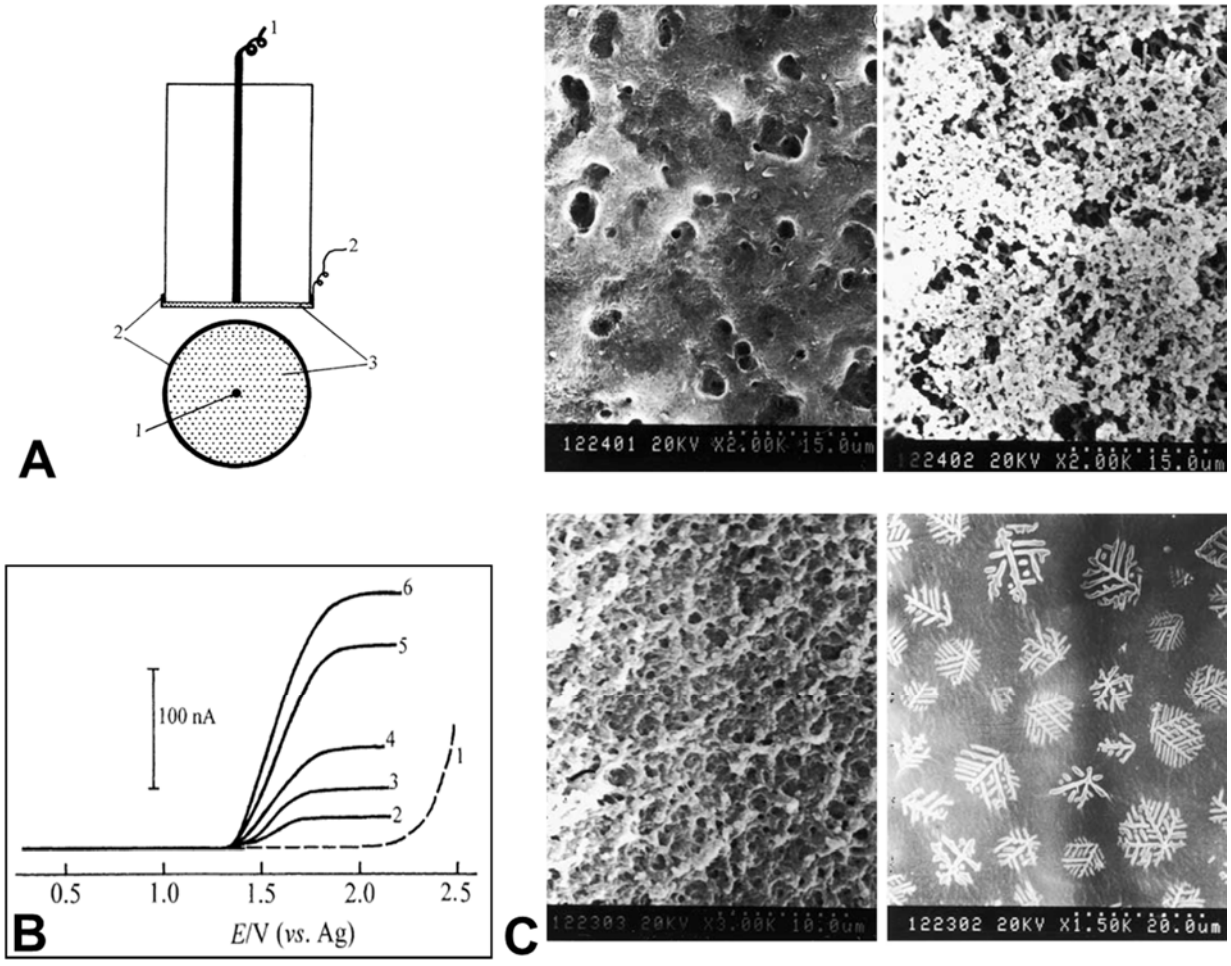

Figure 9. (A) Schematic diagram of full-solid-state microamperometric gas sensors. (1) microdisc working electrode (Au); (2) counter/reference electrode (Ag); (3) PAN-DMSO-TBAP solid polymer electrolyte film. (B) Voltammograms of the CO_2 sensor in CO_2/N_2 gas mixtures. CO_2% v/v: (1) 0; (2) 10; (3) 20; (4) 40; (5) 80; (6) 100. (C) SEM images of the solid electrolyte film (composition of the electrolyte film is the same as that of the corresponding sample mentioned in Table 2). Reproduced with permission from ref (138). Copyright©2001 Elsevier.

with protein antibodies, and they used this device to detect proteins in blood for the first time (139).

Willner *et al.* developed technology to selectively sense endonucleases, enzymes that decompose DNA chain, using a magnetomechanical method with a cantilever (140) (Figure 10).

A research team at Purdue University, USA, developed technology to manufacture a very-high-sensitivity nanocantilever biosensor that spreads an antibody on a surface to detect ultra-trace amounts of pathogens. The team made a cantilever nanobiosensor spreading antibody on the surface by a simple method by dipping the cantilever into a solution containing a specific antibody, and reported that the antibody density became high toward the ends of the nanocantilever. Using this behavior of the nanocantilever, a small-mass material such as a virus with a weight less than an atogram (1×10^{-18} g) can be measured very sensitively.

The result of this study is very meaningful because this study proposed a "miniature pathogen detecting sensor design technique," a new concept involving the introduction of an antibody with strong affinity for a specific virus or bacteria to a nanocantilever. Bashir *et al.* measured one particle of a virus by checking that the resonant frequency shift increased with the number of virus particles (141).

Lechuga *et al.* developed a new sensor by integrating 20 nanocantilevers, 20 emitting lasers, and light-sensing circuitry to coat a target gene within a microfluidics device with a complementary nucleic acid sequence. This portable device can detect cancer-related genetic changes

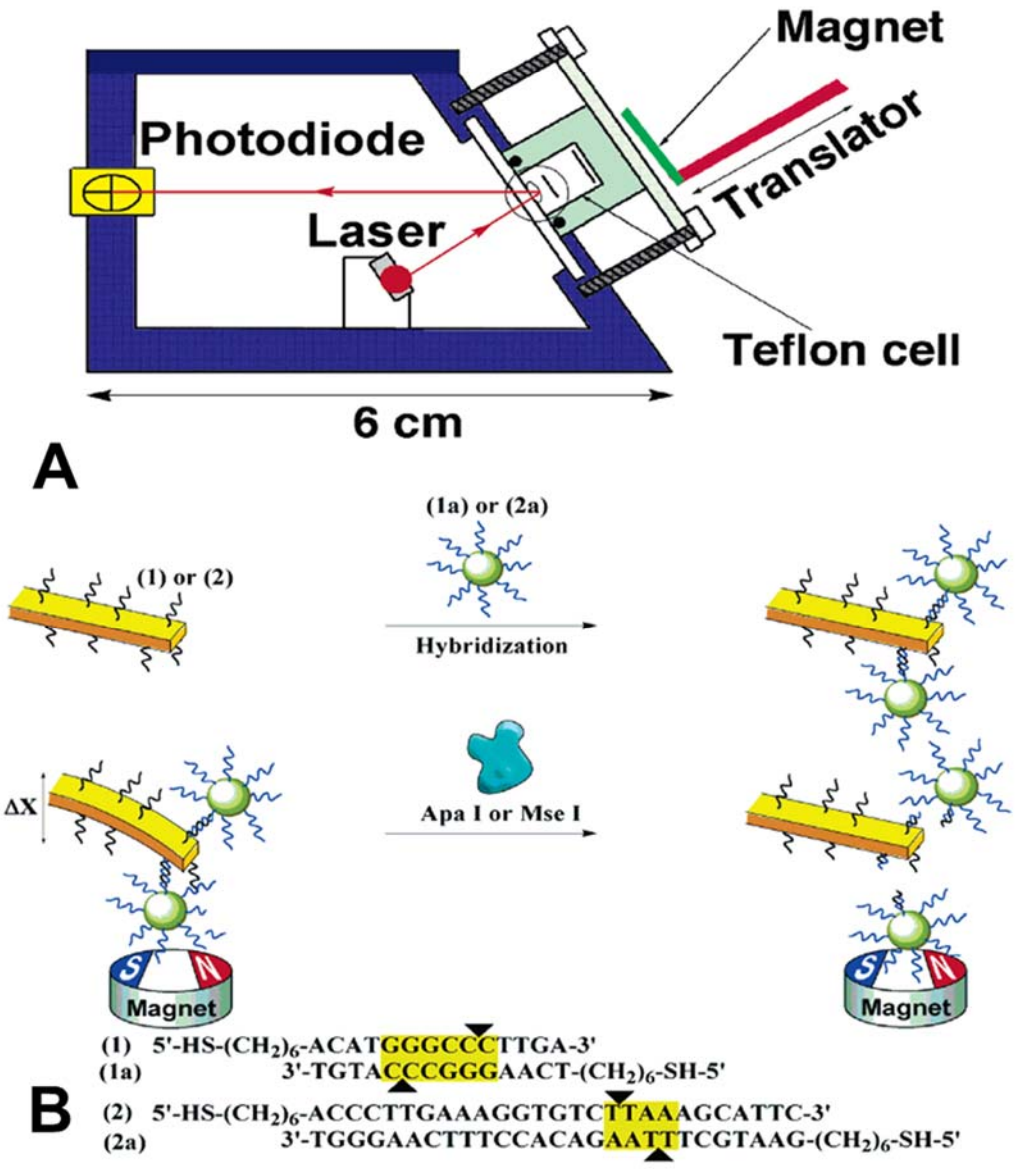

Figure 10. Magnetomechanical detection of endonuclease activities on a functionalized cantilever: (A) instrument setup and (B) magnetomechanical detection of specific endonuclease action. Reproduced with permission from ref (140). Copyright©2010 Elsevier.

Vo-Dinh *et al.* studied nanobiosensors with optical fibers and developed one for the first time in 1987. Currently, theirs is the most advanced technology in the field of optical fiber nanobiosensors. Nanoscale optical fiber biosensor for single cell analysis have successfully been developed using this technology to selectively analyze ultra-trace materials (142–146). With regard to the optical fiber nanobiosensor tip, they made an optical fiber tip having a diameter of 50 nm using a "heat and pull" method to obtain the required thickness by applying heat to a silica optical fiber having a large diameter (600 μm) using a CO_2 laser. This is manufactured by a three-step method in which a chemical process is carried out to fixate the biocognitive molecule after vaporizing aluminum, silver, or gold to a thickness of 100~200 nm on the tip (147). The adhesion of the optical fiber acting as the optical transducer to biomaterial such as fixed acceptors, antibodies, and nucleic acid (DNA) makes it possible to form a covalent bond or chemical sensitivity layer. The manufactured sensor can be used for carrying out measurements at the nano level. The manufactured optical fiber nanobiosensor for analysis of a single cell has a feature to selectively analyze ultra-trace materials. The research group analyzed benzo(a)pyrene tetrol (BPT), a carcinogenic metabolic substance, and

Table 2. Composition of solid polymer electrolyte and their ionic conductivity (σ) at room temperature (138)

Sample no.	PAN (mg)	DMSO (ml) (contain 0.1 mol^{-1} TBAP)	σ (Ω^{-1} cm^{-1})
1	12	0.4	~1 × 10-3
2	20.4	0.4	6.4 × 10-4
3	42.6	0.4	1.9 × 10-4
4	73.2	0.4	6.2 × 10-5

benzo(a)pyrene within a single cell using the antibody nanobiosensor. The nanobiosensor with the developed optical fiber analyzes passing through single animal cells (MCF-7) that are 10 μm in size (146,148). In addition, Vo-Dinh *et al.* developed a nanobiosensor to quantify cytochrome c activity, a protein that plays an important role in cell energy production and apoptosis, as a way to measure environmental carcinogens. In particular, they developed an optical fiber nanobiosensor for various living things such as a device to measure the activity of capsase-9, a biomarker, in the field of cell destruction monitoring (149,150).

Plasmonics nanomaterials used for the detection of biomolecules as metal nanoparticles can simplify the detection and improve the amplification, accuracy, and reliability of the detecting signal of a biosensor. Gold nanoparticles have LSPR optical features by coupling with the electromagnetism of light depending on the form and size, and many high-sensitivity optical biosensors with such features are being developed. For example, Chilkoti *et al.* (151,152), Okamoto *et al.* (153), and Frederix *et al.* (154) carried out non-marking monitoring of biomolecule interactions such as antigen–antibody reaction after physically absorbing gold or silver nanoparticles on a glass surface. Van Duyne *et al.* formed silver nanopatterns in a regular triangular form by a nanolithography method and applied it to high-sensitivity DNA sensing (155–159). Sönnichsen, Reinhard, *et al.* developed a plasmon ruler bisosensor that increases the plasmon coupling effect depending on the distance between the nanoparticle coated with a biomaterial (160–163). El-Sayed *et al.* (164,165) developed a sensor with LSPR optical features formed from a gold nanodisk pair manufactured by lithography. They also developed a new high-sensitivity nanobioanalysis method to combine SPR phenomenon (166–167) formed in gold pattern having larger regular micron sizes than nano sizes on a chip surface using the optical property of gold nanoparticles at a specific wavelength and applied it to DNA detection. With regard to a biosensor with interferometry, Nikitin *et al.* developed an SPR-interferometry method in which an interferometry measuring method was used to measure the beam phase reflected by SPR phenomenon for application to biosensing and chemical measurement (168). This method can be analyzed by the phase change in the interference pattern followed by the change in the thickness of the receptor layer fixed in the particle on the sensor surface, and it exhibits higher sensitivity than existing commercial SPR devices. Wu *et al.* developed a high-sensitivity system by combining heterodyne interferometry with SPR features (169). This system measures the phase change in the SPR phenomenon. It is possible to measure the same by combining a total internal reflection (TIR) device with an existing SPR device. Mirkin *et al.* fixed a short oligomer or antibody to magnetic nanoparticles and gold or silver nanoparticles and developed a bio barcode sensor through a proper combination of the above three materials and successfully applied it to cancer biomarker detection (170). Bailey *et al.* (171,172) detected proteins and nucleic acids with high sensitivity at once by applying an amplification method with gold and silver nanoparticles coated by the 2nd antigen to DNA-encoded antibody libraries (DEAL). Keating *et al.* demonstrated the detection of HIV and SARS virus at once by designing a molecular beacon receptor and developing a new nanooptical biosensor based on nanowire technology (173). Lieber *et al.* manufactured a high-sensitivity biosensor to detect biomaterials by manufacturing a non-marking field-effect transistor (FET) device with a nanowire array coated with antibodies (174).

6. CONCLUSIONS

Biotechnology is one of the most basic and important fields of science because its scope involves human life and related phenomena. It is expected that the field of nanobiotechnology will expand its scope steadily to improve the quality of human life through contributions to various fields such as medical science, pharmacy, environment, public health, military, agriculture, food, and materials science. Nanobiotechnology has been attracting increasing attention in recent years, and it is clearly seen to have great potential in the future. For successful developments in nanobiotechnology, it will be necessary to support academic and industrial efforts and understand the scope of this technology. The field of nanobiosensor technology discussed in this review is being evaluated as a good research index of developments in fusion technology. It is expected that high-sensitivity nanobio technology with previously unrealizable detection limits will be utilized effectively for ultra-trace measurements required in bio measurement, real-time measurement, and *in vivo* measurements.

A biosensor is defined as "a device that detects physiological data and converts it to useful, identifiable signals such as color, fluorescence, and electrical signals by applying or imitating biological elements." Therefore, biosensors include various electronic devices. This review discusses the meaning and importance of studies on nanobiosensors by introducing the features of nanotechnology in a simple manner and by presenting concrete examples of the detection of biomaterials with nanoelectronic devices.

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Send correspondence to: Shin-Won Kang, School of Electronics Engineering, College of IT Engineering, Kyungpook National University, 1370 Sankyuk-dong, Bukgu, 702-701 Daegu, South Korea, Tel: 82-53-940-6829, Fax: 82-53-940-6829, E-mail: swkang@knu.ac.kr

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