Award Accounts

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Nanobiodevices for Genome Analysis, Proteome Analysis, and Biomedical Applications

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Nanobiodevices are developed to analyze biomolecules and cells for genome and proteome analysis. In this article, I describe numerous advantages of nanobiodevices, especially in biological, medical, and clinical applications. I also describe the development of a nanopillar device for the ultrafast separation of DNA and nanoball materials for the fast separation of wide range of DNA fragments. Bacterial cellulose is applied to the separation of DNA and SNPs (single nucleotide polymorphism) analysis of cancer genes for diagnosis of cancer. I developed a new synthetic method for quantum dots (QDs) based on appropriate cluster confirmation by ab initio molecular orbital calculation. QDs are applied to the screening of siRNA, highly sensitive detection of disease related proteins, and development of theranostic device for cancer diagnosis and therapy. Because of the high efficiency of nanobiodevices in the biomolecular and cellular analysis, numerous types of nanobiodevices are developed and applied to the diagnosis of diseases, including cancer, diabetes, hypertension, and infectious diseases.

1. Introduction

Nanobiodevices are contrivances, equipment, machines, or components, which are created by overlapping multidisciplinary activities associated with nanotechnology and biotechnology, intended for biological, medical, and clinical purposes. During the past decade, nanobiodevices have progressively begun to focus on the establishment of main four fields of biomedical applications of nanotechnology, including 1) diagnostic devices, 2) molecular imaging, 3) regenerative medicine, and 4) drug delivery systems. The research efforts in my laboratory have been focused on the development of novel nanodevices, nanomaterials, and nanotechnologies intended for biomedical applications,[1–8] including genome and proteome analysis, analysis of biomolecules and cells, diagnosis of diseases, in vivo imaging, stem cell therapy, tissue engineering, and gene delivery systems, as shown in Figure 1.

Since nanobiodevices have the tremendous advantages listed in Table 1, they are applicable to fast analysis of biomolecules developed by appropriate small space, which have short diffusion distance biomolecules, with extremely small diffusion constants. Highly sensitive detection and single molecular analysis will be possible by use of nanobiodevices, because of the large surface to volume ratio and the use of extremely small volume, such as fL (10^{-15} L) and aL (10^{-18} L). Nanobiodevices are also suitable for single molecular and single cellular manipulation, since laminar flow, which is characteristic of low Reynolds number (*Re*) micro- and nanofluidics, is valuable for separation and manipulation of single biomolecules and single cells, and it is possible to fabricate the nanostructure and nanomaterials, of which the size is comparable to the size of biomolecules and cells. Nanomaterials, such as quantum dots, which have quantum confined effects, are essential to develop highly bright and long life fluorescence materials even in the near infrared region, which will be indispensable for molecular imaging and in vivo imaging.

We have developed numerous nanobiodevices as shown in Figure 1. In this Award Accounts, I will describe some of our research achievements, including nanodevices for genome and proteome analysis,[3–6,9,10] self-assembled nanomaterials for biomolecular analysis,[4–6,11–14] biomedical application of quantum dots,[7,8,15–25] and clinical applications of nanobiodevices.[1,26–32]

2. Nanobiodevice for Biomolecular, Genome, and Proteome Analysis

We have established a nanofabrication technology, which is combined electron beam lithography and plasma dry etching, to fabricate nanostructures with high aspect ratio on quartz glass chips as shown in Figure 2.[4–6,9] In this work, we developed pillar nanostructures, called nanopillars, which are defined as column-like structures of which diameter or diagonal is less than 1000 nm and height greater than diameter or diagonal (an

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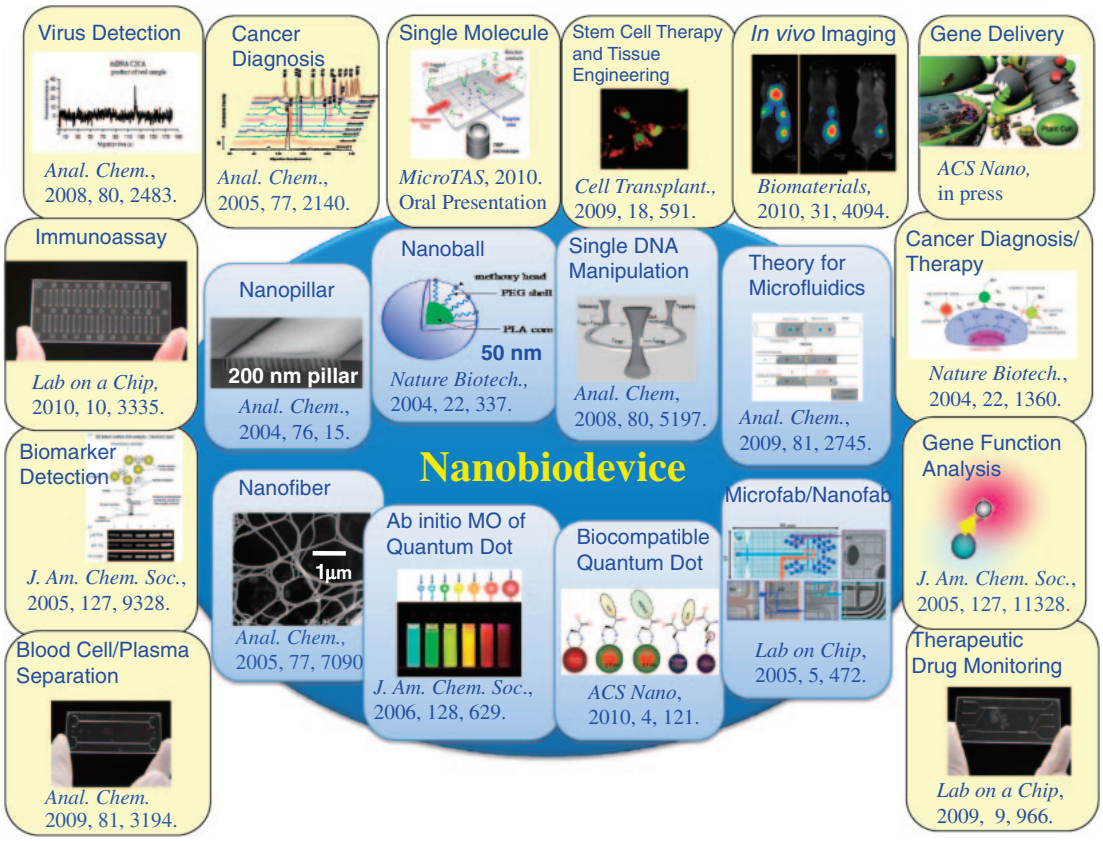

Figure 1. Development of nanobiodevices and biomedical applications.

Table 1. Advantages in Nanobiotechnology

1)	Short distance to diffuse $t \approx x^2/D$ ($D = 10^{-7}$ cm^2 s^{-1}), $t = 10^7$ s ($x = 1$ cm), $t = 10^{-1}$ s ($x = 1$ μm)
2)	Large surface to volume ratio
3)	Suitable for single molecular events Especially $K_d >$ nM–μM 1 mL = (1 cm)^3 (×1.6 zM) 1 fL = (1 μm)^3 (×1.6 nM), 1 aL = (100 nm)^3 (×1.6 μM)
3)	Manipulation of conformation for biomolecule DNA(1 nm–cm), Protein (1–10 nm)
4)	Laminar flow to manipulate a single cell $Re = xv\rho/\eta = 0.01$–100 (Laminar flow at $Re < 2000$)
5)	Mimic the chemical environment of a cell
6)	Quantum confined effects $E = E_g + \pi^2(a_B/a)^2R_y - 1.786(a_B/a)R_y - 0.248R_y$

aspect ratio over preferably 2). Although the nanofabrication with high aspect ratio on glass substrates is particularly difficult in comparison with nanofabrication on the silicon substrate, the nanofabrication technology we developed is applicable to the fabrication of l00-nm diameter nanopillars with the aspect ratio over 20. In semiconductors, nanostructures with lower aspect ratio are useful for developing high-speed processors and high-capacity memory, since the semiconductor is manipulating the electron, the photon, and the hole. In contrast, high aspect ratio nanostructures are highly desirable for nanobiodevices, since the sizes of biomolecules and cells range from nm to μm.

The nanopillar arrays 100–500 nm in diameter and 500–5000 nm long were designed and fabricated inside a microchannel several μm wide and 500–5000 nm deep, and applied to the separation of DNA as shown in Figure 2. The spacing between nanopillars is controlled at 500 nm and achieved 30-s separation of λDNA (48 kbp (kilo base pair)) and T4 DNA (166 kbp) by using a 380-μm long microchannel, since the spacing is almost comparable to the λDNA radius in an aqueous solution. The speed of separation by the nanopillar chip is at least 100 times faster than gel electrophoresis and 30 times faster than capillary electrophoresis. The 500-nm spacing nanopillar is applicable to the separation of smaller DNA, including 2, 4.4, 6.6, 9.4, and 23 kbp. Longer time is needed (640 s) to separate all DNA fragments in this case, since the DNA are smaller than the 500-nm spacing of the nanopillars and a longer microchannel (7.9 mm) is required to revolve such DNA fragments.

The effect of nanopillar array arrangement is examined as shown in Figure 3 and we found use of the tilted arrangement of nanopillar arrays enables gel electrophoresis like separation of DNA as shown in the left figure of Figure 3 and Figure 2, that is smaller DNA fragments migrate faster than larger ones. The square arrangement of the nanopillar array gives fast separation of DNA as shown in the right figure of Figure 3, but surprisingly, the larger DNA fragments migrate faster than the smaller. To understand the separation mechanism, we developed a technology to image a single DNA molecule migrating in the nanopillar array channel in real time. Single molecule imaging of DNA inside the tilted arrangement of nanopillar

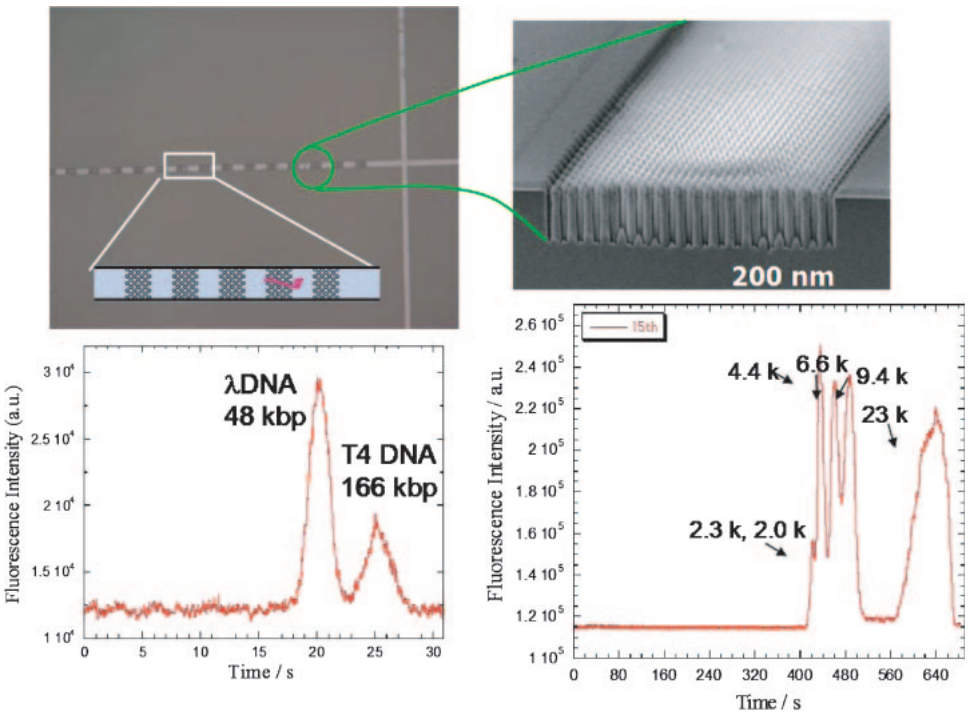

Figure 2. Fast analysis of DNA by nanopillar device.

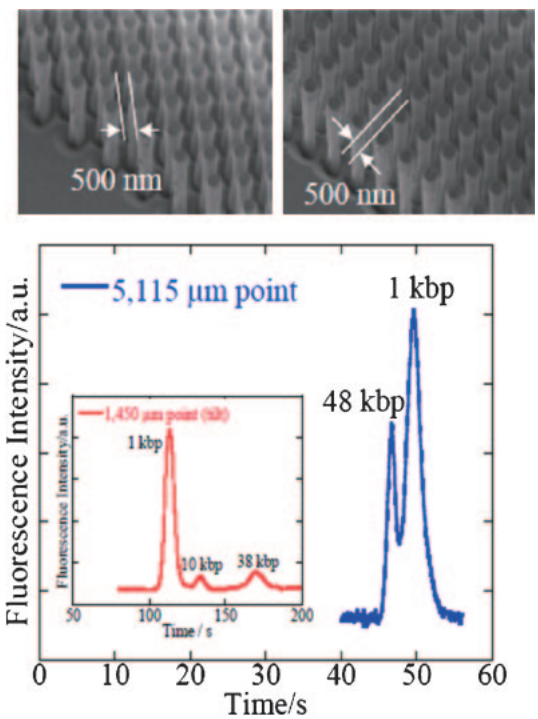

Figure 3. Effect on DNA separation of nanopillar arrangement.

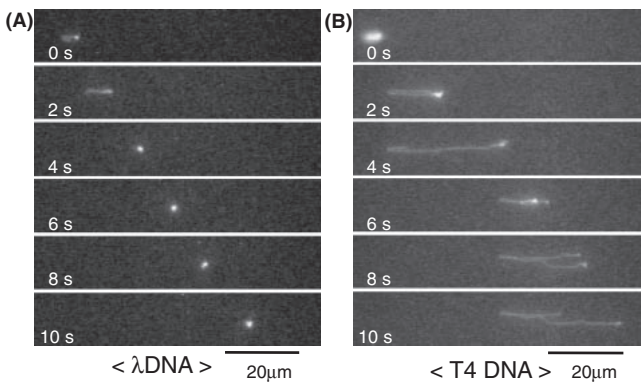

Figure 4. An imaging of a single DNA molecule migrating in the nanopillar device.

array demonstrates that the DNA fragment, which is smaller than the spacing of nanopillars, maintains random coiled conformation during the migration as shown in Figure 4A, but in contrast, the DNA fragments larger than the spacing frequently loops around the nanopillars, extends to a U-shape, and relaxes to a random coiled conformation as shown in Figure 4B. Such continuous conformational change of the larger DNA fragment due to collision with nanopillars results in the longer migration time than the shorter DNA fragment. The similar single molecule imaging in the square arrangement of nanopillar array illustrates that the longer DNA fragments keep an extended conformation of DNA inside the nanopillar array and migrate faster than the smaller fragments, of which is similar to the image in Figure 4A. In conclusion, the change in the nanopillar arrangement controls the separation order of DNA, since it is possible to control the conformation of DNA.

Nanotechnology coupled with MEMS (micro electro mechanical systems), enables development of nanotweezers to manipulate a single DNA molecule as shown in Figure 5.[10] The diameter of the top of the nanotweezers is about 5 nm, which is twofold larger than the diameter (2 nm) of DNA and the tweezers will be able to open and close as a actuator based on MEMS

technology. A single DNA molecule is successfully captured by the ends of the nanotweezers as shown in Figure 5 and it is easy to manipulate even a single DNA molecule. This technology will be applicable to measure the electric current for a single DNA molecule, to read DNA sequences, and MEMS gene delivery systems.

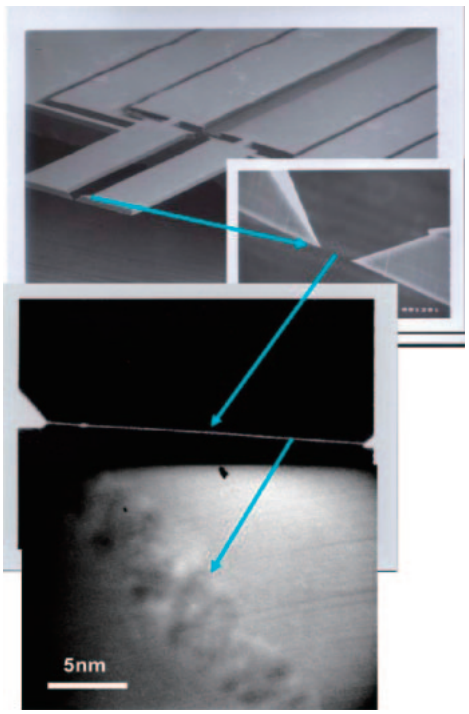

Figure 5. Manipulation of a single DNA molecule by nanotweezer.

3. Self-Assembled Nanomaterials for Biomolecular Analysis

Although nanofabrication based on semiconductor techniques is apparently powerful technology to develop novel nanobiodevices as described above, we have another influential nanofabrication technique, that is self-assembly to fabricate the nanostructures, based on chemistry and polymer science. We developed nanoballs as shown in Figure 6 for the fast separation of DNA by using microfabricated microchannels.[4–6,11] The diameter of the nanoball structure, which is fabricated by the self-assembled micelle of PEG–PLA copolymer, is precisely controlled in the range of 20–300 nm by controlling the length of PEG. An aqueous solution of nanoballs, which has low viscosity comparable to that of water, is easily introduced into a microchannel (100 µm wide and 50 µm wide). After a DNA sample is injected into the microchannel, the separation of DNA is achieved within 60–100 s by applying 70 V. Using a nanoball solution, the high-resolution separation of DNA ranging from 100 bp to 15 kbp is achieved. To understand the separation mechanism, we performed imaging of a single DNA molecule migrating in a nanoball solution as shown in Figure 7. The results demonstrate that a DNA molecule in a nanoball solution forms an intramolecular globule conformation, which is unique in a nanoball solution. An induction of such unique conformation by a nanoball solution may be one of the reasons why we achieved better resolution of DNA fragments. Nanoball structures with other materials, such as PEGylated latex,

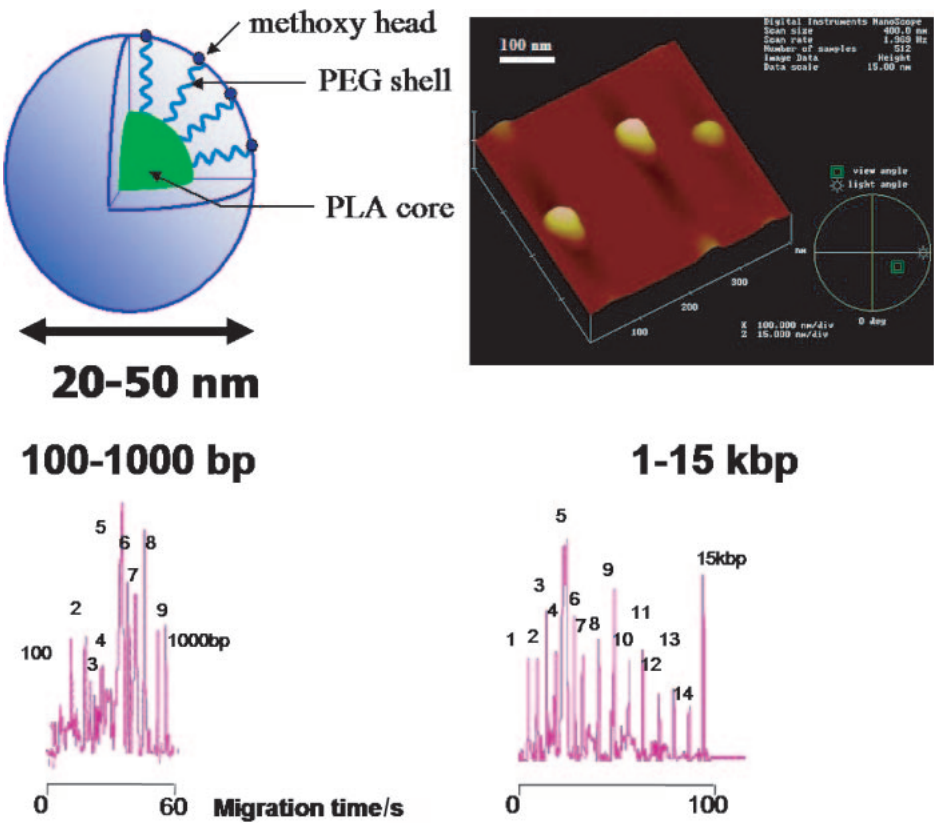

Figure 6. Structure of nanoball and DNA separation by a nanoball solution.

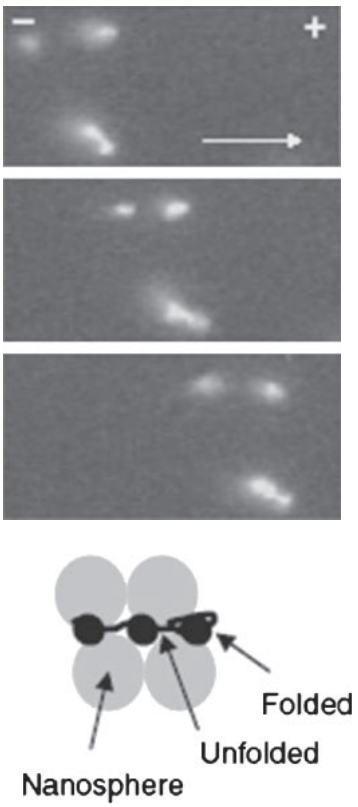

Figure 7. An imaging of conformational change in single DNA molecules in a nanoball solution.

have been found to achieve the high-resolution separation of DNA.[12]

We found some natural nanostructures, such as bacterial cellulose, are suitable to analyze DNA fragments as shown in Figure 8.[13,14] Bacterial cellulose, of diameter less than 50 nm, makes a gel-like network in an aqueous solution as shown in the picture of Figure 8 and it is easy to control the pore size of the network, which is appropriate for the separation of DNA. The separation of DNA fragments from 100 bp to 15 kbp is achieved with high-speed and high-resolution. This technique is applied to cancer diagnosis based on the detection of SNPs (single nucleotide polymorphism) of cancer gense and has realized ultrafast diagnosis of cancer within 60 s.[14] A coupling of optical characteristics of a compact disc (CD) and a solution of bacterial cellulose enhances the detection sensitivity of DNA as shown in Figure 9.[13] Only the simple introduction of a bacterial cellulose solution inside a microchannel covered by a CD gained tenfold enhancement in fluorescence detection of DNA and the enhancement mechanism is explained by optical confined effects.

4. Biomedical Applications of Quantum Dots

Semiconductor nanocrystals, quantum dots (QDs), are an excellent example of nanomaterials that show their potential ability for biomedical applications of nanotechnologies.[7,8] Tremendous physicochemical properties of QDs such as bright photoluminescence and high photostability are attributed to their small size, shape, and chemical composition. There has been increasing use of QDs in medicine for purposes of diagnosis, imaging, and gene delivery. In recent years, these

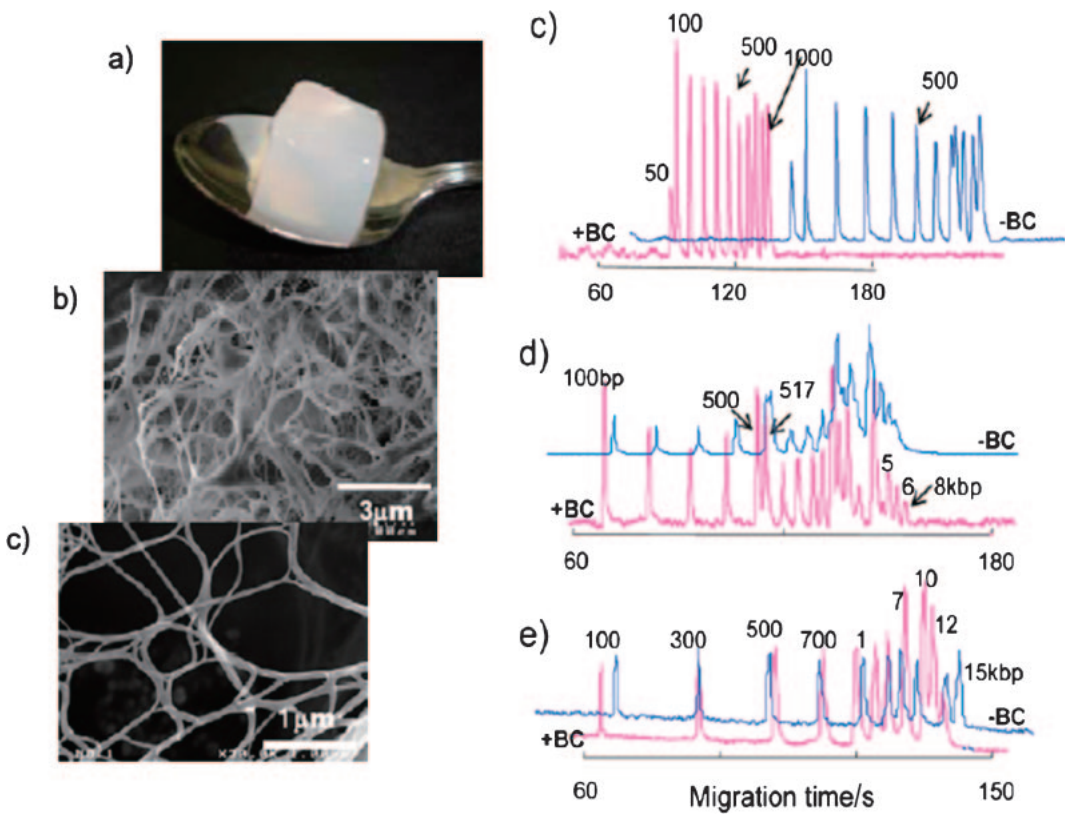

Figure 8. SEM images of bacterial cellulose nanofiber and DNA analysis by a nanofiber solution.

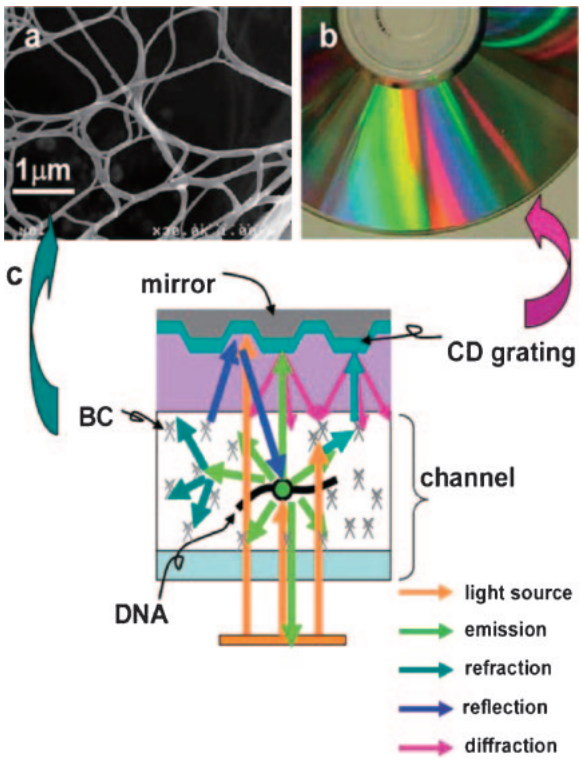

Figure 9. Sensitivity enhancement of DNA by a nanofiber solution on a compact disc.

unique properties of QDs coupled with nanobiodevices have been initiating evolutional changes in single-molecule techniques. Single-molecule measurements have provided a wealth of information and have allowed better understanding of a wide range of physical, chemical, and biological phenomena and processes.

Ab initio molecular orbital calculation revealed that the cluster structure of CdSe as shown in Figure 10 is essential to obtain high intensities of fluorescence of QDs.[19] According to MO calculation we have developed new a synthetic method for QDs and gained QDs with excellent optical properties as shown in Figure 10.[19–25] Additionally, we developed a method to immobilize numerous biomolecules and functional molecules on QDs as shown in Figure 11,[15–18] and these QD conjugated materials are applied to a wide variety of biomedical applications, including screening of siRNA by measuring the FRET intensity, highly sensitive detection of low abundant proteins related to diseases, cancer cell detection, theranostics of cancer, single molecular measurements of enzymatic reactions, evaluation of gene delivery systems, and in vivo imaging of stem cells.[7,8,15–18,25]

The screening of efficiency of siRNA is realized by measuring the FRET signal between QDs-labeled siRNA and Cy5-labeled mRNA as shown in Figure 11. We designed and synthesized several sequences of siRNA, of which sequences are complementary to the sequences of BCR-ABL fusion gene. This gene is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). Since the length of siRNA is usually 20 bases and

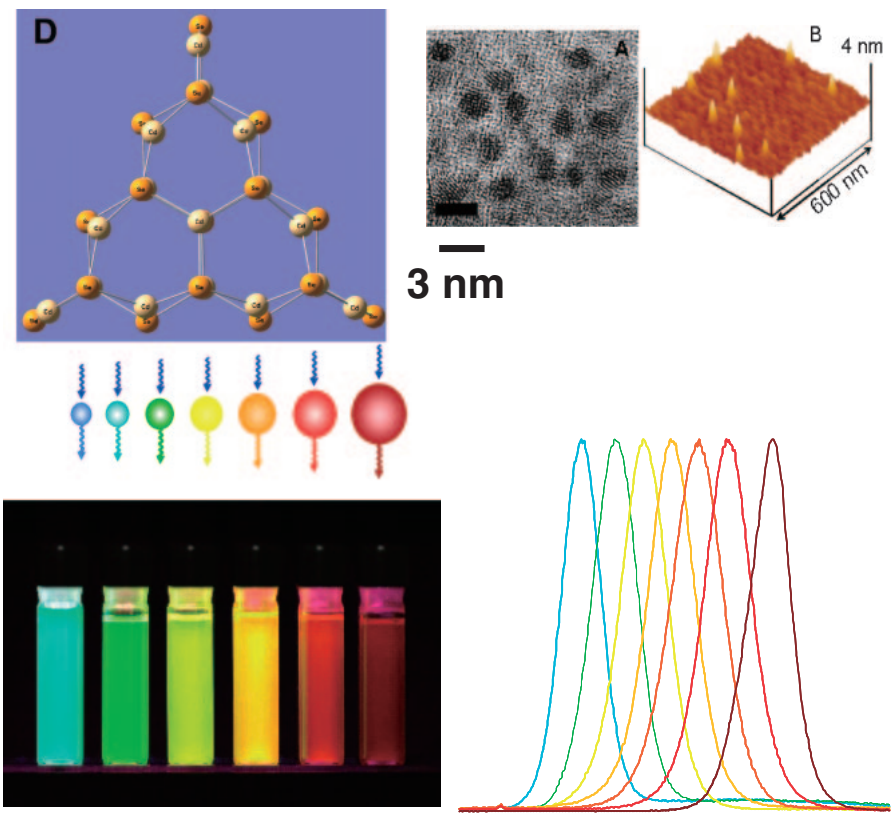

Figure 10. Structure of quantum dots and their fluorescence spectra.

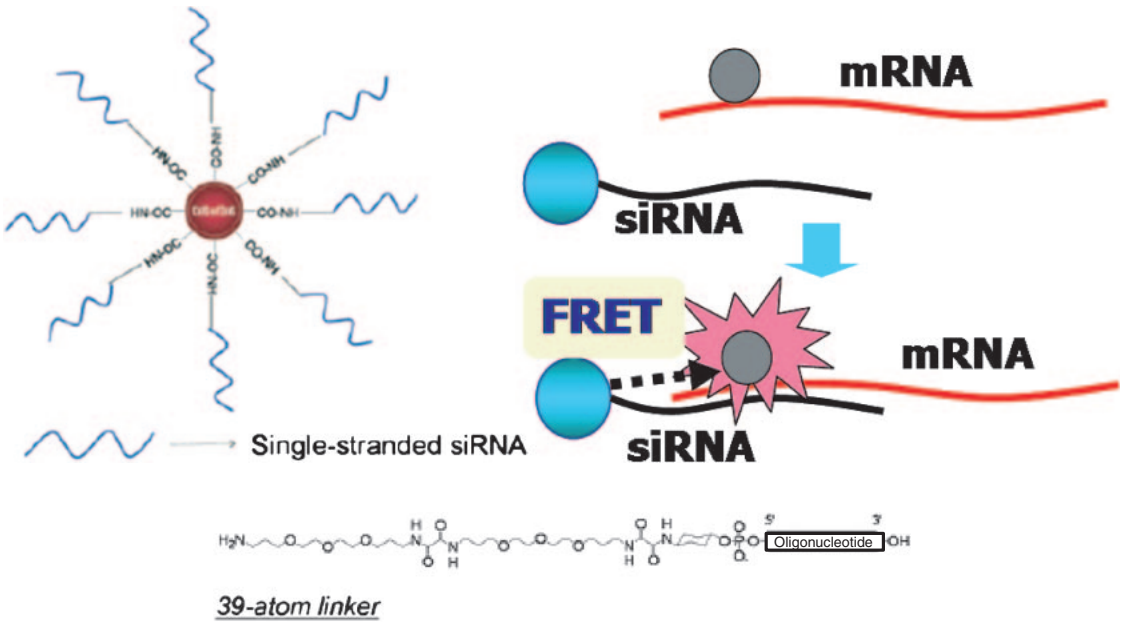

Figure 11. Screening of siRNA by FRET (fluorescence resonance energy transfer) between quantum dot-labeled siRNA and Cy5-labeled mRNA.

the size of the target gene is over tens of thousands of bases, it is hard to find the most appropriate sequence of siRNA, which expresses the most efficient gene silencing effects. Several candidate sequences of siRNA are synthesized and immobilized on the QDs. The mRNA of BCR-ABL fusion gene is extracted from leukemia cells and labeled with Cy5. When the interaction between siRNA and mRNA occurs, the distance between QDs and Cy5 is smaller than the Forester distance, which is 5 nm in this experiment, and as strong FRET signal is obtained. We found the FRET signal intensities for the interaction between mRNA and the different sequences of siRNA is linearly correlated to the efficiency of the gene-silencing ability of siRNA.[18] This illustrates that the FRET technology based on QDs is extremely useful for the screening of the most appropriate sequence of siRNA.

The QDs are applied to the highly sensitive detection of TRF1 (telomeric repeat binding factor) and Tin2 (TRF1-interacting nuclear protein 2), which are related to leukemia. Since both proteins are expressed in the extremely lower level of concentration, it is hard to detect them even by ELISA, which is the most highly sensitive technique to detect proteins. To detect such proteins, we synthesized biotinylated QDs and biotinylated antibody and a mixed a solution of avidins, biotinylated QDs, and biotinylated antibody, and added to the gel membrane on which the separated target protein is transferred. As shown in Figure 12, numerous QDs are bound to a single antibody bridged by avidins. This QD-based technique enables detection of even 300 pg of proteins, of which sensitivity is a hundred-fold larger than that of ELISA.[17]

Lectin-immobilized QDs are selectively bound to the sugar chain on cancer cell membranes, since there is a specific sequence of sugar chain expressed on the cell. As a result, we can detect a small number of cancer cells through QDs selectively bound to the cell as shown in Figure 13.[15,16] This technology is applicable to the early stage diagnosis of cancer. In addition, we found long irradiation of 400-nm light for 30-min induces the apoptosis of the cancer cells, whereas the normal cells are alive during the irradiation of 400-nm light. The 400-nm light is usually used to excite QDs to gain high fluorescence intensity. Long irradiation may accelerate production of reactive oxygen species, which may induce the apoptosis of cancer cells. This technology gives us novel technologies, such as "theranostic" devices, which means the fusion of therapy and diagnosis.[15]

5. Clinical Applications of Nanobiodevices

We developed numerous nanobiodevices for biomedical and clinical applications collaborating with professors and physicians at Nagoya University hospital and University of Tokushima hospital as well as industrial co-workers, including Panasonic, TORAY, Toshiba, Fujitsu, NGK, AsOne, Cluster, Agilent, and Shimadzu as listed in Table 2.[26–32]

Nanobiodevices are applied to diagnosis of hypertension by the fast analysis of SNPs of hypertension related genes and diagnosis of lung cancer through the detection of deletion of the specific sequence for the lung cancer related genes. Injection diseases are diagnosed by the sensitive and fast detection of bacterial DNA by devices integrated by DNA amplification and DNA analysis. We developed an immunoassay device applicable to cancer diagnosis. Nanodevices for protein expression analysis are applied to cancer diagnosis and drug screening. We also developed other types of nanodevices for diagnosis of diabetes, cancer, hypertension, and stress through the detection of blood glucose, sugar chain structure, cholesterol, amylase activity, telomerase activity, and cancer cells. These applications are extremely useful developing low invasive and ultrafast diagnosis of diseases by using small devices for point-of care technology.

Nanobiodevices enable development of powerful technologies for biomedical applications, but the clinical applications of

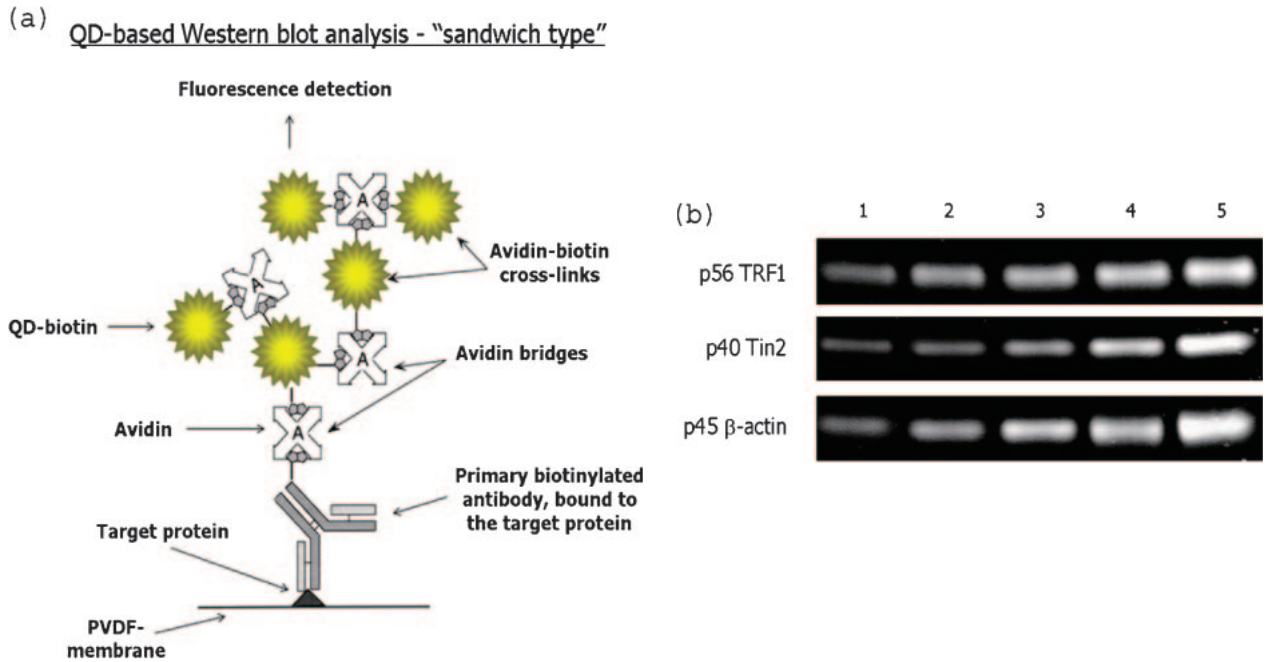

Figure 12. Ultra sensitive detection of leukemia related proteins by quantum dot-based immunoassay.

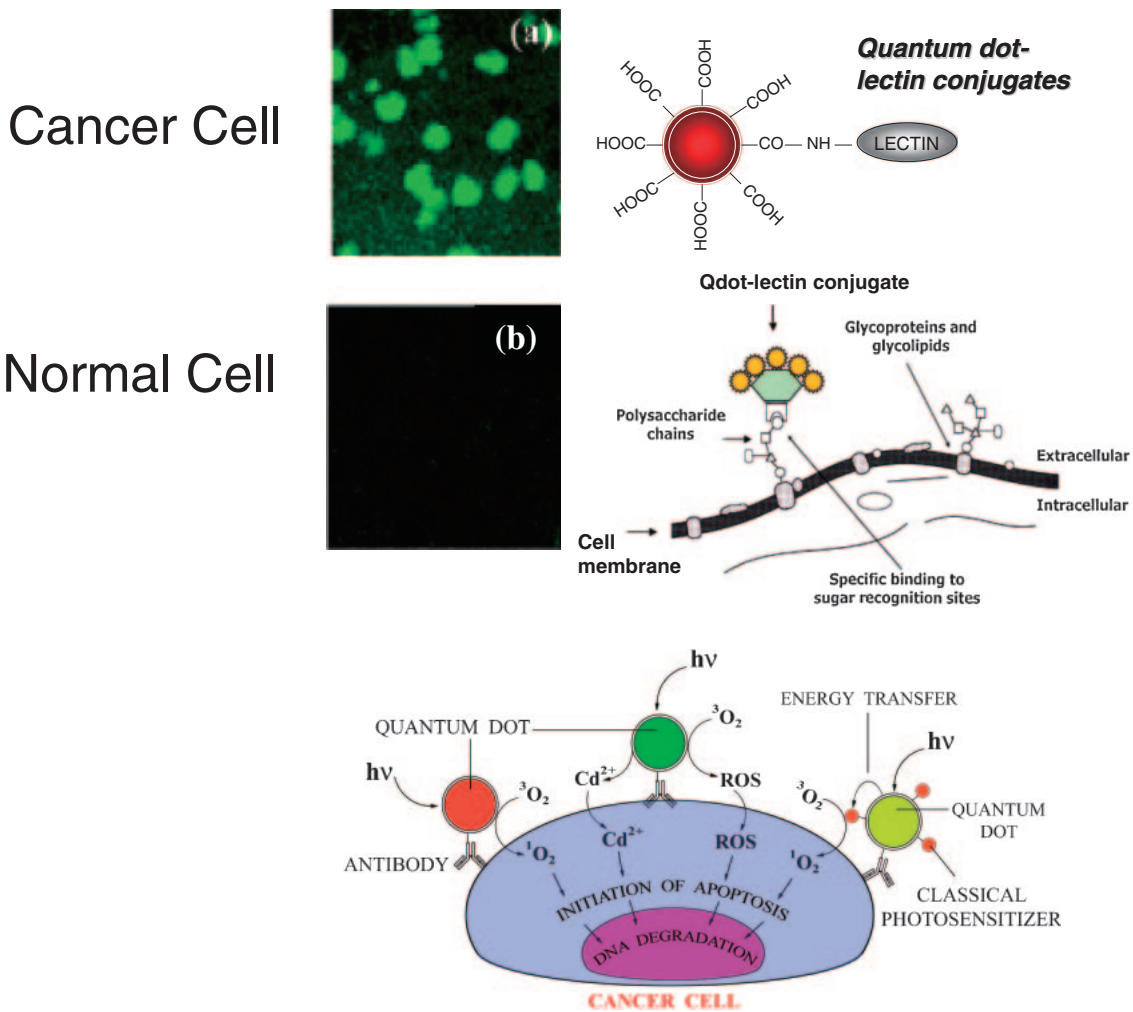

Figure 13. Theranostics of cancer by quantum dot.

Table 2. Biomedical and Clinical Applications of Nanobiodevices

Analysis	Disease diagnosed	Analysis time/s	Sample	Literature
Genome	Cancer	50	Cell	*Nat. Biotechnol.* **2004**
SNPs	Hypertension	60	Blood	*Anal. Chem.* **2005**
Deletion	Lung cancer	100	Blood	*Anal. Chem.* **2005**
Bacteria DNA	Infection	200	Blood	*Anal. Chem.* **2008**
Protein expression	Cancer	15	Cell	*Anal. Chem.* **2003**
Immunoassay	Cancer	20	Cell	*Anal. Chem.* **2007**
Protein expression	Drug screening	15	Cell	*J. Proteome Res.* **2004**
Blood sugar	Diabetes	120	Blood	*Electrophoreis* **2007**
Sugar chain structure	Cancer	80	Cell	*Anal. Chem.* **2006**
Cholesterol	Hypertension	100	Blood	*Anal. Chem.* **2005**
Amylase	Stress	180	Blood	*Electrophoresis* **2007**
Telomerase	Cancer	60	Cell	*Electrophoresis* **2005**
Cell sorter	Cancer	60	Cell	*Electrophoresis* **2005**

nanobiodevices are still limited. Although technological development for first-generation nanobiodevices is mature, the limitation of clinical applications is caused by severe clinical regulations, including international standardization, toxicity issues, preclinical trials, clinical trials, and establishment of clinical guidelines for the technology to develop. In the clinical application of DNA chips, which is a good example of a nanobiodevice, the technology development of DNA chip was largely mature by the late 1990s, but it took another 15 years before the first FDA approval of DNA chips in 2009. Academia and industry worldwide have made tremendous efforts for clinical regulations for DNA chips during the last decade.

The most important clinical applications for nanobiodevices are DNA-based diagnosis of diseases, blood biomarker detection, gene delivery systems, molecular imaging, and regenerative medicine. The technology developments of the first-generation nanobiodevices for these clinical applications are mature and efforts toward clinical approval have started. I hope the clinical applications of nanobiodevices will expand over the next decade.

For the development of second-generation nanobiodevices, we still need to develop technologies for single molecular detectability for DNA-based diagnosis of diseases, higher-sensitivity, such as fM or aM blood biomarker detection, integration of gene delivery systems and molecular imaging toward theranostic nanodevice development, and three-dimensional tissue construction for regenerative medicine.

6. Conclusion

In conclusion, nanobiodevices, which have tremendous advantages, are powerful technology for developing low invasive and highly sensitive detection of disease marker proteins in whole blood to apply to disease diagnosis. Nanobiodevices are essential to develop novel technology such as theranostic devices and nanorobots for an integration of diagnosis and therapy for future personalized medicine.

The work summarized here was achieved by the dedicated efforts of staff, post-docs, students, the Applied Analytical Chemistry Laboratory at Nagoya University, the Physical Chemistry Laboratory at University of Tokushima, and the Single-Molecule Bioanalysis Laboratory, Health Technology Research Center, and Health Research Institute at National Institute of Advanced Industrial Science and Technology (AIST). I would like to thank all co-workers in the authorship of relevant references. This work was supported by grants from Japan Science and Technology Agency (JST), Japan Society for the Promotion of Science (JSPS), and NEDO.

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